Dissertation On

ANALYTICAL STUDY OF CORRELATION BETWEEN PLASMA D-DIMER LEVELS AND LYMPHOVASCULAR INVOLVEMENT IN OPERABLE CARCINOMA BREAST

Dissertation submitted

in partial fulfillment of the requirements for the degree of

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GENERAL SURGERY

STANLEY MEDICAL COLLEGE

THE TAMILNADU Dr.MGR MEDICAL UNIVERSITY

CHENNAI-TAMILNADU

MAY 2019

CERTIFICATE

This is to certify that, the dissertation titled **"ANALYTICAL STUDY OF CORRELATION BETWEEN PLASMA D-DIMER LEVELS AND LYMPHOVASCULAR INVOLVEMENT IN OPERABLE CARCINOMA BREAST"** is the bonafide work done by **Dr.MONIKA.S** Postgraduate student (2016-2019) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my guidance and supervision ,in partial fulfillment of the requirements of The TamilnaduDr.MGR Medical University Chennai for the M.S. Degree Branch I General Surgery Examination tobe held in May 2019.

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DECLARATION

I **Dr.MONIKA.S,** solemnly declare that this dissertation titled **"ANALYTICAL STUDY OF CORRELATION BETWEEN PLASMA D-DIMER LEVELS AND LYMPHOVASCULAR INVOLVEMENT IN OPERABLE CARCINOMA BREAST"** is a bonafide work done by myself in the Department of General Surgery, Government Stanley Medical College Hospital, Chennai under the guidance and supervision of our unit chief and Our Head of the department

I also affirm this work was not submitted by myself or any others for any award, degree to any other University either in India or elsewhere. This is submitted to The Tamilnadu Dr.M.G.RMedical University, Chennai in partial fulfillment of the rules and regulations for the award Master of Surgery Degree Branch I (General Surgery).

Place:

Date: **Dr.MONIKA.S**

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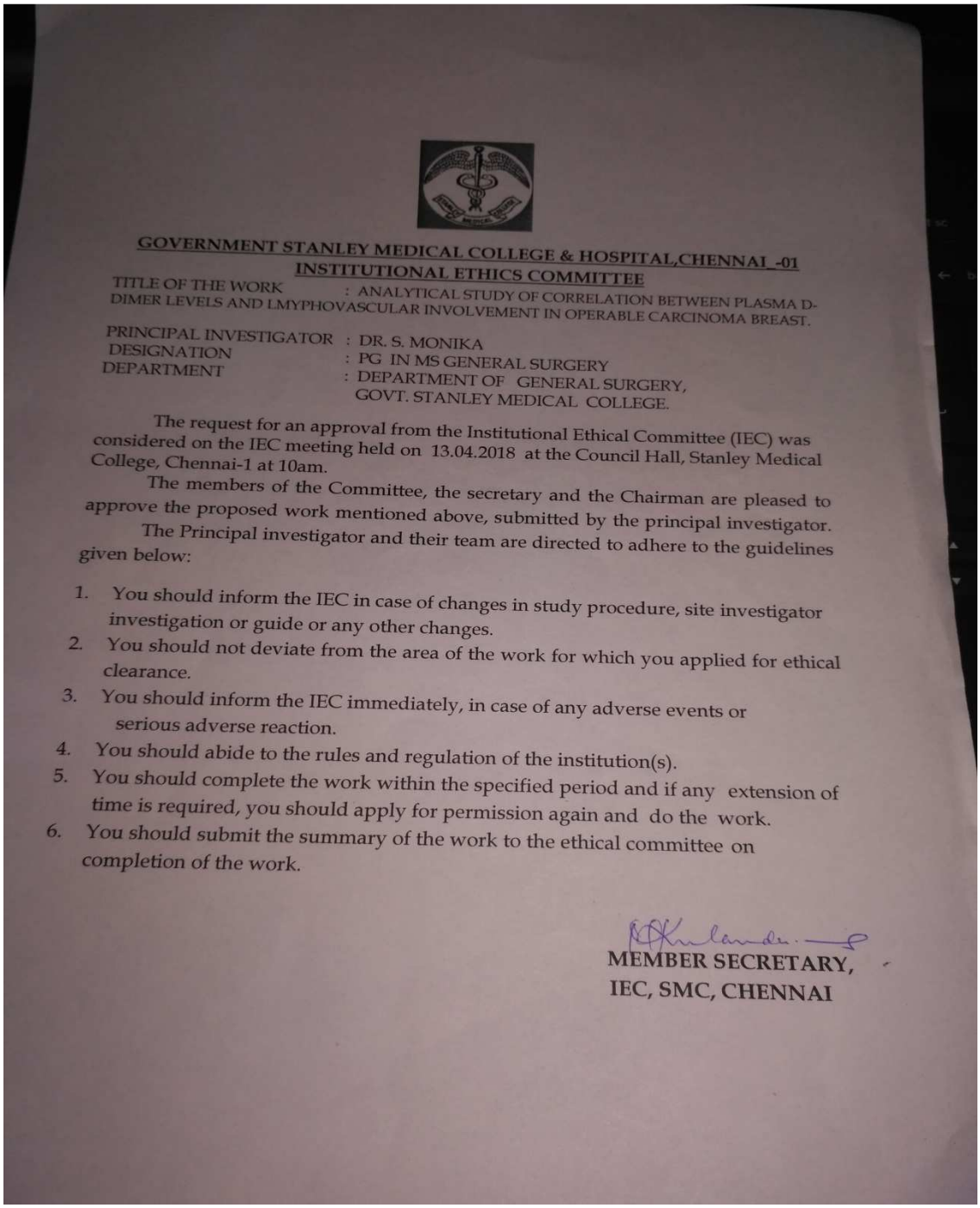
ETHICAL COMMITTEE APPROVAL LETTER



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PRINCIPAL INVESTIGATOR : DR. S. MONIKA
DESIGNATION : PG IN MS GENERAL SURGERY
DEPARTMENT : DEPARTMENT OF GENERAL SURGERY, GOVT. STANLEY MEDICAL COLLEGE.

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CONTENT

INTRODUCTION

1. INTRODUCTION

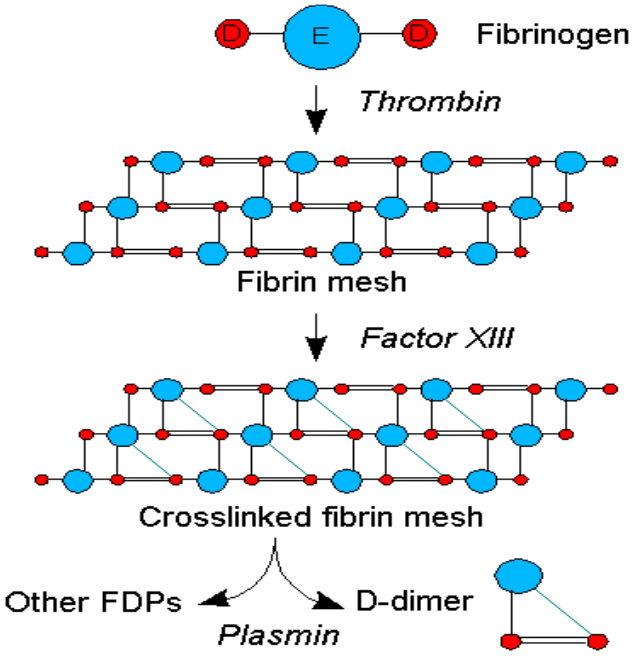
The relationship between malignancy and thrombosis is known for over manyyears[1]. In almost half of the cancer patients, thromboembolism is present,which is detected at autopsy. Thrombosis in cancer often is migratory, may involve superficial veins and relatively unusual sites. The hypercoagulable state in malignancy is due to a complex interaction of tumor cells and their products with the host cells, leading to various degrees of impairment of the normal defense mechanisms that ordinarily protect the host against thrombogenesis[2]. Tumor cells activate directly the blood clotting cascade and cause thrombosis or can induce procoagulant environment and inhibit the anticoagulant properties of the vascular endothelial cells, platelets, monocytes and Macrophages.[1]

There is evidence that the components of the coagulation/ fibrinolytic system play an important role in cancer biology and angiogenesis. Fibrin deposition and remodeling in extracellular matrix of the tumor is an important initial step in tumor metastasis. For a tumor to successfully metastasize from its primary location, it must undergo several obligate steps, including the invasion into either the lymphatic or vascular lumen, transportation through the circulation, and establishment of viability in target tissues. Cross linked fibrin in

the extracellular matrix serves as a stable framework for endothelialcell migration during angiogenesis and tumor cell migrationduring invasion.

Various abnormalities, including thrombocytosis, an increase in fibrinogen and fibrin degradation products like D-dimer, a rise in factors V,VII,VIII , IX, and XI levels, and a decrease in antithrombin III , are seen in cancer patients[3].

D-dimer (or D dimer) is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two D fragments of the fibrin protein joined by a cross-link. The cross-link between two D fragments remains intact, however, and these are exposed on the surface when the fibrin fragments are sufficiently digested. The structure of D-dimer is either a 180 kDa or 195 kDa molecule of two D domains, or a 340 kDa molecule of two D domains and one E domain of the original fibrinogen molecule.



D-dimers are not normally present in human blood plasma, except when the coagulation system has been activated, for instance because of the presence of thrombosis or disseminated intravascular coagulation. The D-dimer assay depends on the binding of a monoclonal antibody to a particular epitope on the D-dimer fragment. D-Dimer is detected by various laboratory methods, mostly used is based on a different monoclonal antibody against D-dimer. The binding of the antibody is then measured quantitatively by one of various laboratory methods.

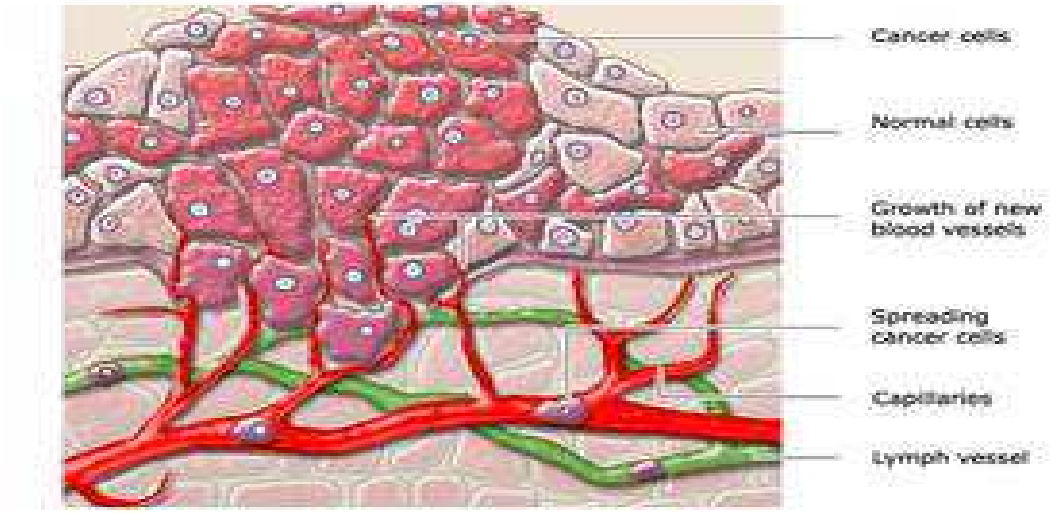
Breast cancer is the most common cancer in women causing death.

The three most important prognostic factors in operable carcinoma breast are lymph node status, primary tumor size, and tumor grade.

Plasma D-dimer is a hypercoagulability and fibrinolytic system marker and is increased in patients with various solid tumors.

It has been indicated that an interaction between angiogenesis and hemostasis may facilitate metastasis in breast cancer and that plasma D-dimer levels are a measurement of matrix remodeling in the tumor[4]. Elevated levels of circulating D-dimer have been correlated with an enhanced progression of the disease and a reduced overall survival in metastatic breast cancer[5]. D-dimer assessment constitutes a attempt to consider a product of fibrin degradation as a specific marker related to the extent of breast cancer in humans.

Several studies has been done to prove this finding, correlating fibrinolytic activity associated with increased D-dimer levels cancer breast patients.[6]



Vascular endothelial cells injury caused by toxins released from fast growing tumor cells and the fibrinolytic activation on the surface of tumor cells, cancer patients often exhibit abnormalities in coagulation and fibrinolytic activities and their D-dimer levels tends to be higherthan those in non-neoplastic populations.[1]

AIMS AND OBJECTIVE

2. AIMS AND OBJECTIVES

- To evaluate pre-operative D-dimer level in Operable Carcinoma of Breast and post operative histopathology report for lymphovascular involvement.

- To evaluate role of D-dimer in patients of operable carcinoma breast, in predicting lymph node metastasis in carcinoma patients and to look for relationship of these markers with histopathologic parameters which are known to have prognostic value in carcinoma breast.

HISTORICAL BACKGROUND

3.HISTORTICAL BACKGROUND

Humans have been known about Cancer of the breast for a long time. The medical text of Edwin Smith Surgical Papyrus which describes cases of breast cancer, dates back to 3,000–2,500 B.C.E.

People made offerings in the shape of a breast to the god of medicine; in Ancient GreeceAnd Hippocrates in early 400s B.C.E described the stages of breast cancer.

Around first century A.D., doctors experimented with surgical incisions made over the breast to destroy tumors, and thought that breast cancer was associated with the end of menstruation. This theory might have prompted the association of cancer with older age.

In the beginning of the Middle Ages, medical progress was associated with religious philosophies. Christians thought surgery was barbaric and were in favor of faith healing. Meanwhile, Islamic doctors reviewed Greek medical texts to learn more about the breast cancer.

The Renaissance saw a revival of surgery as doctors began exploring the human body. John Hunter is known as the Scottish father of investigative surgery, identified lymph as a cause of breast cancer.

Lymph is the fluid which carries white blood cells throughout the body. Lumpectomies were also performed by surgeons, but there was no anesthesia yet. So, Surgeons had to be fast and accurate to be successful.

The modern approach to breast cancer treatment and research started forming in the 19th century.

1882: William Halsted performed the first radical mastectomy. This surgery was the standard operation to treat breast cancer until into the 20th century.

1895: The first X-ray was taken. Eventually, low-dose X-rays called mammograms were used to detect breast cancer.

1898: Marie and Pierre Curie discovered radium and polonium. Initially, radium was used in cancer treatment.

1932: Modified Radical Mastectomy was developed. This surgical procedure was not as disfiguring as radical mastectomy and becomes the new standard.

1937: Radiation therapy is used in addition to surgery to spare the breast. After removing the tumor, needles with radium are placed in the breast and near lymph nodes.

1978: The drug tamoxifen was approved by the Food and Drug Administration (FDA) for use in breast cancer treatment. Tamoxifen is an antiestrogen drug originally developed for birth control. It’s the first in a new class of drugs called selective estrogen receptor modulators (SERMs) used against cancer.

1984: Researchers discovered a new gene in rats. The human version, called HER2, was found to be linked with more aggressive breast cancer when overexpressed. This cancer is called HER2-positive breast cancer and is not as responsive to treatments.

1985: Researchers discover that women with early-stage breast cancer who were treated with a lumpectomy and radiation have similar survival rates to women treated with only a mastectomy.

1986: How to clone the HER2 gene was discovered.

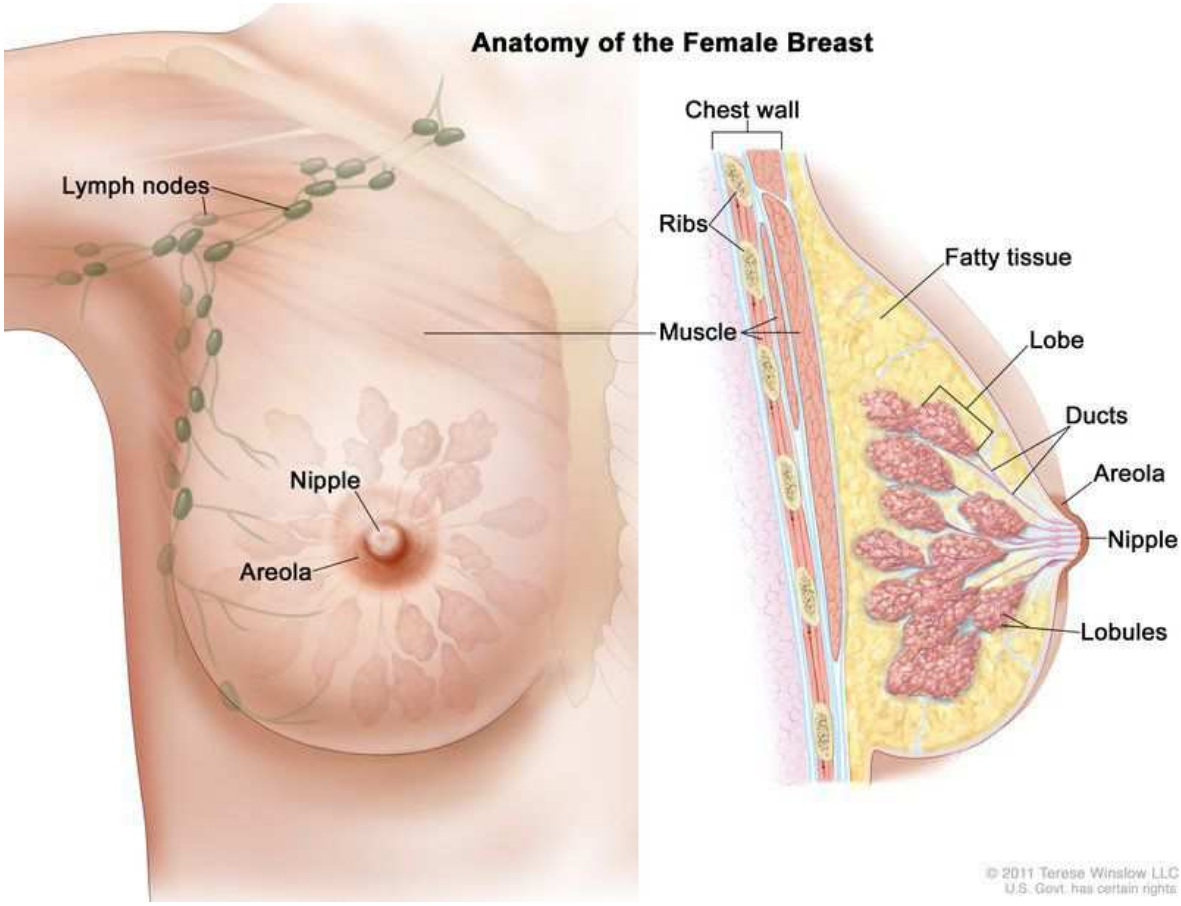
1995: Cloning the tumor suppressor genes BRCA1 and BRCA2. Inherited mutations in these genes can predict an increased risk of breast cancer.

1996: FDA approved Anastrozole as a treatment for breast cancer. This drug blocks the production of estrogen.

1998: Tamoxifen is found to decrease the risk of developing breast cancer in at-risk women by 50 percent, approved by the FDA, it is used as a preventive therapy. Trastuzumab, a drug used to target cancer cells over-producing HER2, is also approved by the FDA.

2006: The drug raloxifene foundto reduce breast cancer risk in postmenopausal women who are at higher risk. It has lower chance of serious side effects when compared with tamoxifen.

SURGICAL ANATOMY

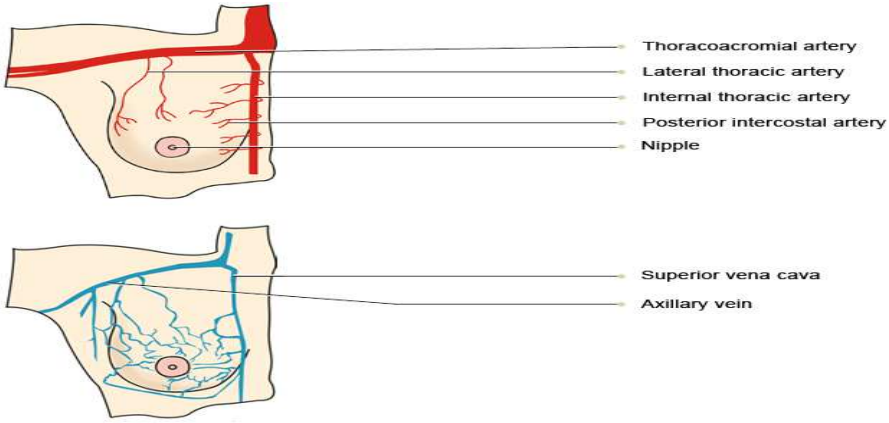


The breast is a skin appendage which develops from modified sweat glands deep to the nipple. Accessory breast tissue may occur along a line from groin to axilla. The development of the rudimentary breast is stimulated by hormones, and commences as a nodule or breast bud deep to the areola in early puberty. The adult breast lies predominantly on the deep fascia of pectoralis major and extends from the second to the sixth costal cartilages. Medially, it extends almost to the midline and laterally it continues as the axillary tail of the breast over the lateral edge of pectoralis major into the axilla.

Superficially, it is separated from the skin by subcutaneousfat, except over the areola and the nipple. The breast substance consists of glandular tissue and surrounding fat. Alterations in hormonal levels cause structural and functionalchanges in the breast during pregnancy, lactation and, to a lesser extent, throughout the menstrual cycle.

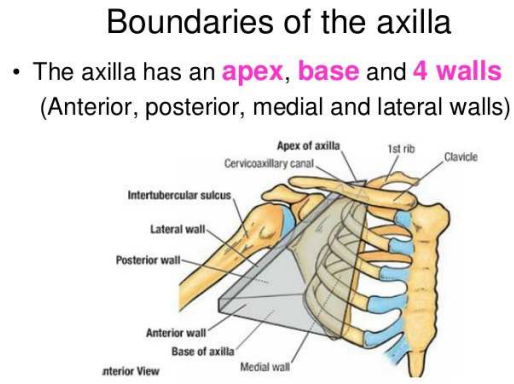
The blood supply of the breast :branches of the internal thoracic (mammary) artery and the intercostal arteries which pierce the intercostal muscles, and laterally from branches of the lateral thoracic artery.

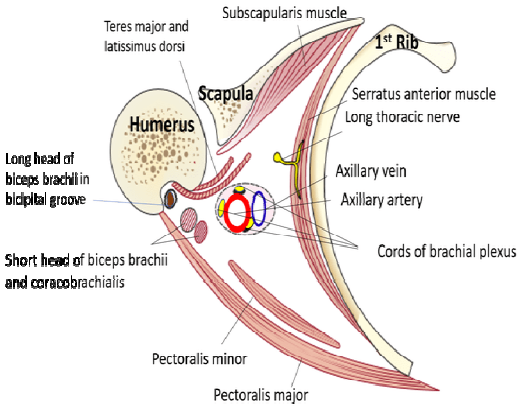
The lymphaticdrainage of the breast follows all these routes, but the predominantdrainage is to the axillary lymph nodes. There issignificant drainage to the internal thoracic nodes from the medial breast.



THE AXILLA:

The axillary contents are the fat and lymph nodes bounded by the axillary walls. The medial wall is bounded by the chest wall covered with serratus anterior. The anterior wall of the axilla is formed by the pectoral muscles and the clavipectoralfascia. The posterior wall comprises latissimusdorsi, teres major and subscapularis





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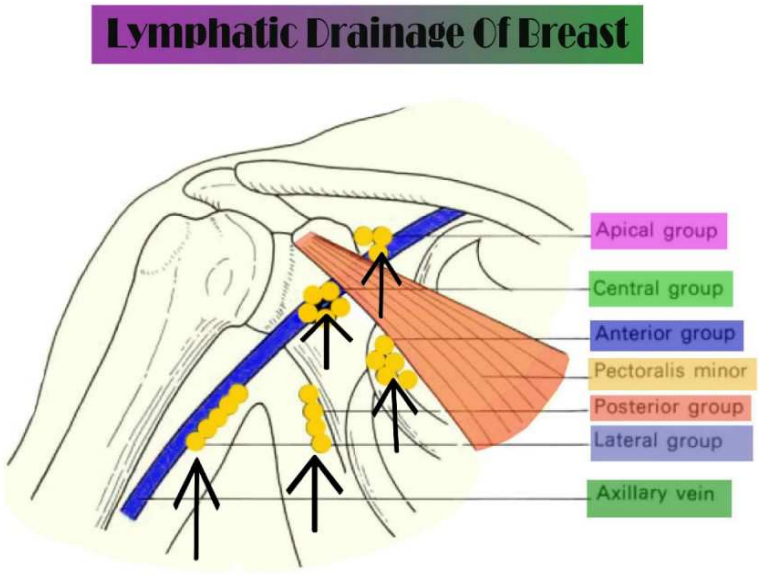
LYMPHATIC DRAINAGE OF THE BREAST:

The axillary lymph nodes lie in the fat of the axilla and receive lymphatic drainage from the upper limb and the superficial tissue of the chest wall in addition to the breast. Lymphatic channels from the breast drain predominantly first to the nodes lowest in the axilla, and then subsequently to the higher nodes, and finally through the apex of the axilla to the supraclavicular nodes.

The axillary nodes are arbitrarily divided into levels I, II and III dependent upon their relationship to the pectoralis minor muscle. Level I nodes are lateral and below the muscle, level II nodes are behind it, and level III nodes are above and medial.

As in malignant melanoma , there is increasing appreciation that the lymph node drainage of the breast is first to one or more specific nodes called sentinel nodes. These are usually in the axilla but they can be in the internal thoracic chain or, more rarely, within the breast itself.



Level 1-Lateral to lateral border of pectoralis minor

• Anterior (Pectoral)

• Posterior (Subscapular)

• Lateral (Brachial)

Level 2-Behind pectoralis minor

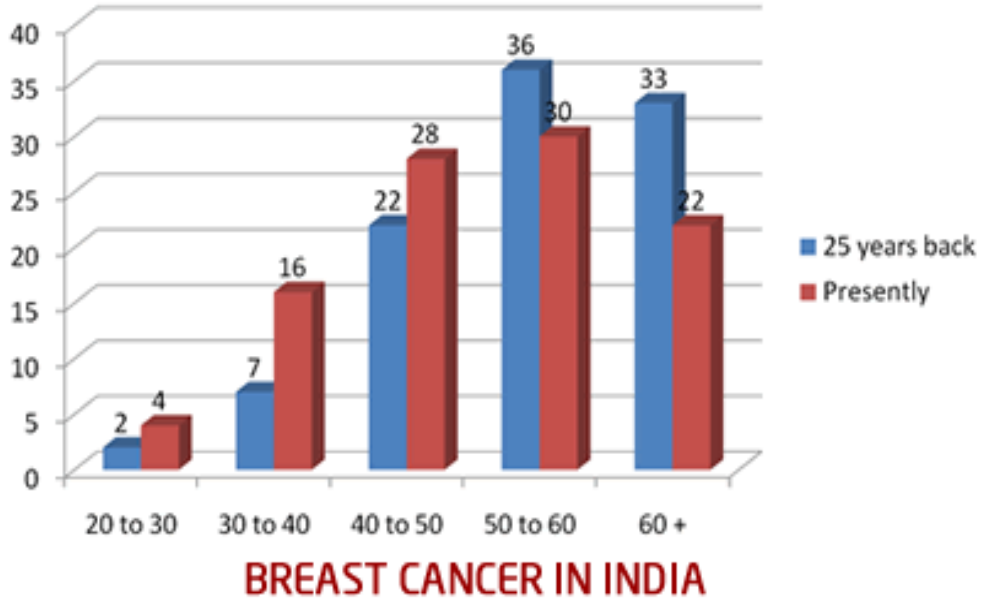
• Central

• Rotters

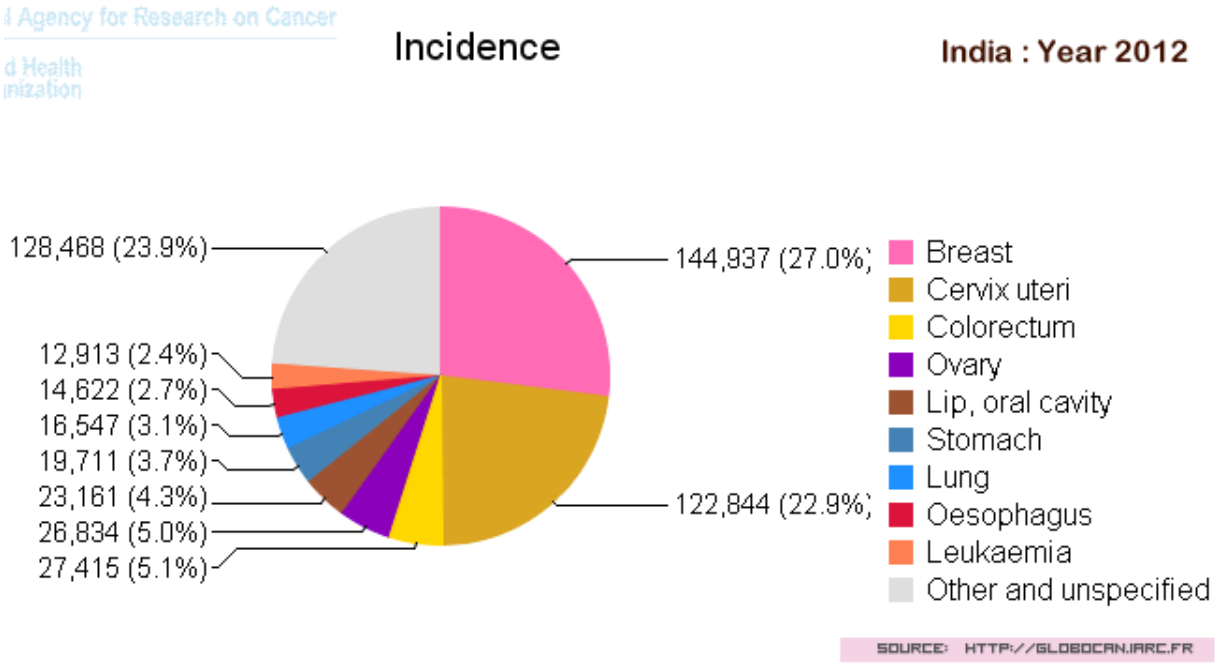
Level 3-Medial to medial border of pectoralis minor

• Apical (Infraclavicular)

EPIDEMIOLOGY:



Breast cancer continues to be the leading cause of cancer in women,by causing 40,000 deaths annually. Morethan 1 million cases of breast cancer diagnosed worldwide each year, making Breast Carcinoma a global health problem. The overall incidence of breast cancer was rising until approximately 1999 because of increases in the average life span, lifestyle changes that increase the risk for breast cancer, and improved survival from other diseases. The rates began to decrease from 1999 to 2006 by approximately 2%/year. This decrease has been attributed to a reduction in the use of HRT after the initial results of the Women's Health Initiative were published but may also be the result of screening mammography .



70.1% of women 40 years and older were screened in 2000 versus 66.4% in 2005. Survival rates in women with breast cancer have steadily improved over the last several decades, with 5-year survival rates of 63% in the early 1960s, 75% from 1975 to 1977, 79% from 1984 to 1986 and 90% from 1995 to 2005. The largest decrease in death rates caused by breast cancer have been in women younger than 50 years (3.2%/year), although they have also decreased in women older than 50 (2%/year).

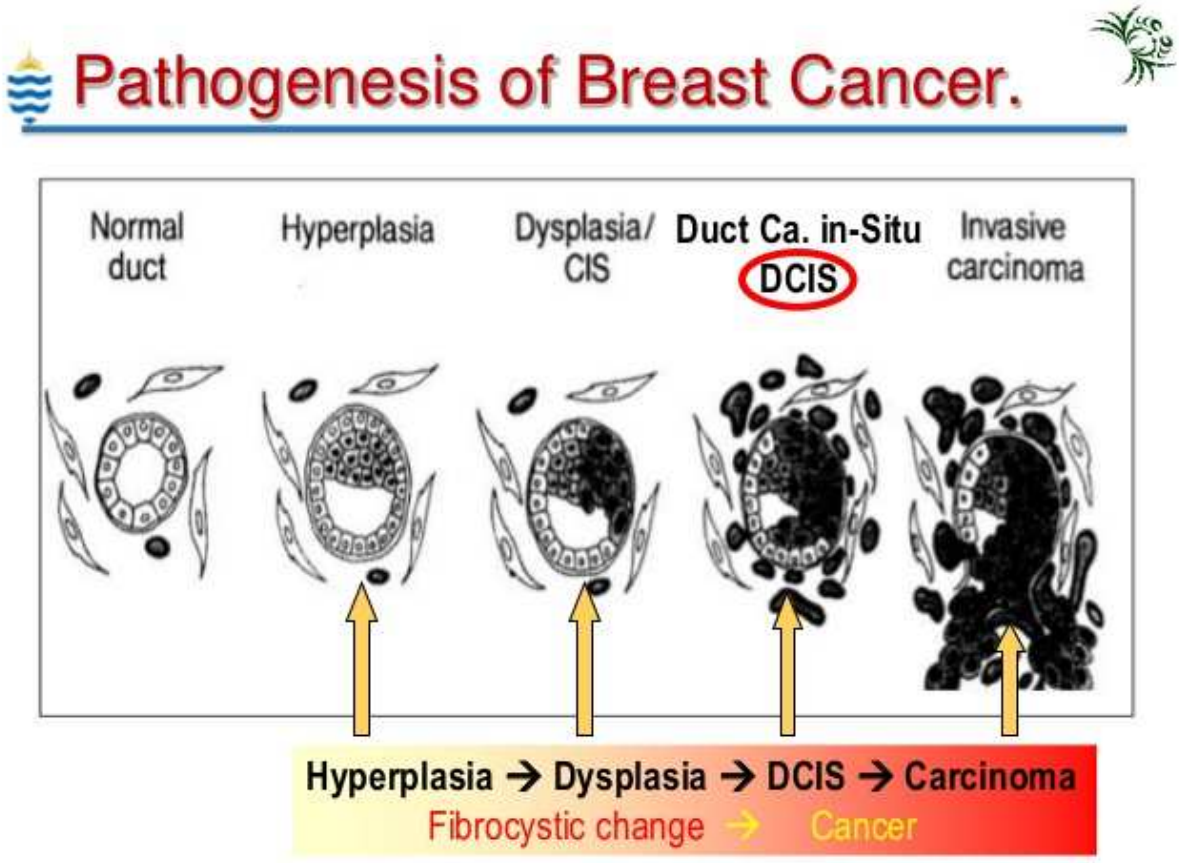
The decreased mortality from breastcancer is thought to be the result of earlier detection via mammographicscreening, improvements in therapy, and a decreased incidence of breast cancer.

The current treatment of breast cancer is guided by pathology, staging, and recent insights intobreast cancer biology. There is an increased emphasis on defining disease biology and status in individual patients, with the subsequent tailoring of therapies toward that individual.

RISK FACTORS OF CARCINOMA BREAST:

Risk Factors That Cannot be Modified
Increasing age
Female gender
Menstrual factors
Early age at menarche (onset of menses prior to age 12 yr)
Older age at menopause (onset beyond age 55 yr)
Nulliparity
Family history of breast cancer
Genetic predisposition (*BRCA1* and *BRCA2* mutation carriers)
Personal history of breast cancer
Race, ethnicity (white women have increased risk compared with others)
History of radiation exposure
Risk Factors That Could be Modified
Reproductive factors
Age at first live birth (full-term pregnancy after age 30 yr)
Parity
Lack of breast-feeding
Obesity
Alcohol consumption
Tobacco smoking
Use of hormone replacement therapy
Decreased physical activity
Shift work (night shifts)
Histologic Risk Factors
Proliferative breast disease
ADH
ALH
LCIS

PATHOLOGY



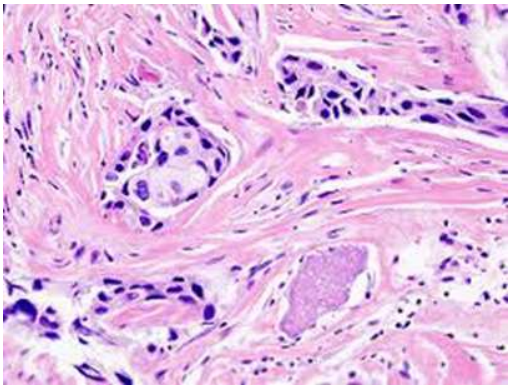
Noninvasive Breast Carcinoma:

Noninvasive neoplasms divided into two major types, LCIS and DCIS .

LCIS was initially believed to be a malignant lesion, but is now regarded more as a risk factor for the development of breast cancer. LCIS is recognized by its conformity to the outline of the normal lobule, with expanded and filled acini. **DCIS** is a more heterogeneous lesion morphologically, and pathologists

recognize four broad categories—papillary, cribriform, solid, and comedotypes. DCIS is recognized as discrete spaces filled with malignant cells, usually with a recognizable basal cell layer made up of presumably normal myoepithelial cells. The four morphologic categories of DCIS are rarely seen as pure lesions, but in reality are often mixed. The papillary and cribriform types of DCIS are generally of lower grade and may take a longer period of time to transform to invasive cancer. The solid and comedo types of DCIS are generally higher grade lesions.

INVASIVE DUCTAL CARCINOMA:



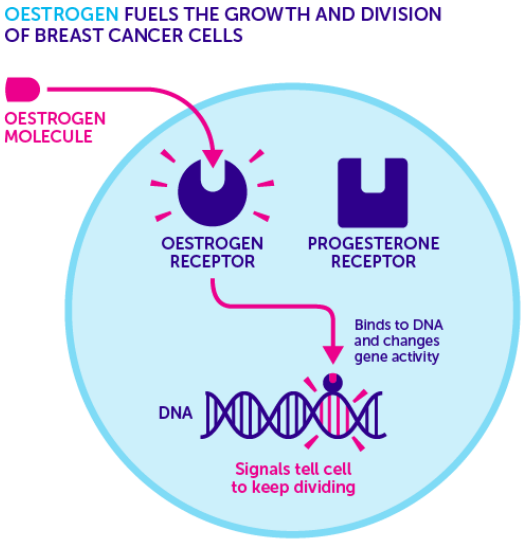
Invasive ductal cancer, also known as infiltrating ductal carcinoma, is the most common form of breast cancer; it accounts for 50% to 70% of invasive breast cancers. When this carcinomadoes not have any specific features, it is called infiltrating ductal carcinoma. Invasive lobular carcinoma accounts for up to 10% of breast cancers, and mixed ductal and lobular cancers have been

increasingly recognized and described in pathology reports. When infiltrating ductal carcinomas take on differentiated features, they are named according to the features that they display.

If the infiltrating cells form small glands lined by a single row of bland epithelium, they are called infiltrating tubular carcinoma. The infiltrating cells may secrete copious amounts of mucin and appear to float in this material. These lesions are called mucinous or colloid tumors. Both tubular and mucinous tumors are usually low grade (gradeI) lesions and represent about 2% or 3% each of invasive breast carcinomas.

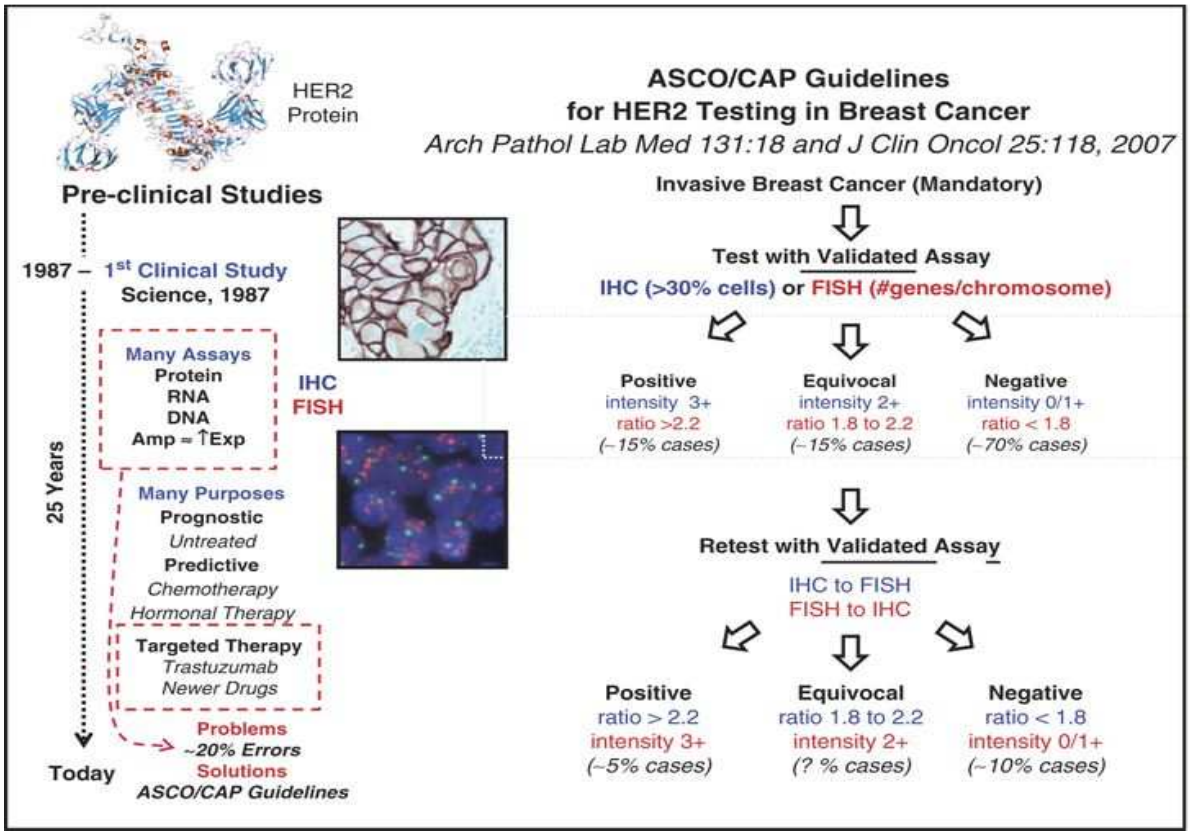
The different histologic subtypes of breast cancer have some relationship with prognosis, although this is influenced by tumor size, histologic grade[7], hormone receptor status, HER-2 status, lymph node status, and other prognostic variables [8]. Infiltrating ductal carcinoma, not otherwise specified (NOS), is the most common form of breast cancer. Its prognosis is variable, modified by histologic grade and expression of molecularmarkers. Basal-like cancer, or medullary cancer in older classifications, is commonly an aggressive form of breast cancer and, because it is triple receptor–negative, there are no targeted treatmentsfor this form of cancer. Infiltrating lobular breast cancers carry an intermediate prognosis, whereas tubular and mucinous cancers have the best overall prognosis.

Molecular Markers and Breast Cancer Subtypes:



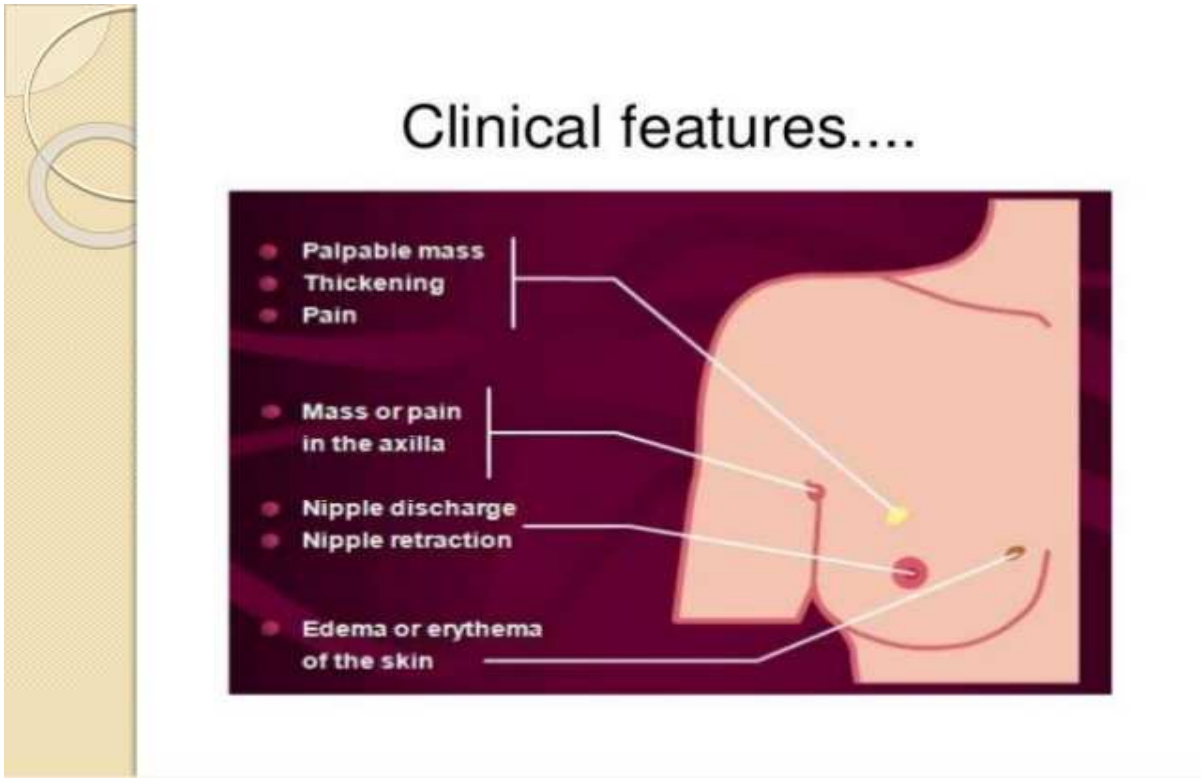
Estrogen receptors and progesterone receptors may be found in breast cancer cells. Cancer cells with these receptors depend on estrogen and related hormones, such as progesterone, to grow. Estrogen and progesterone influence many hormonal functions in women, such as breast development. IHC testing can detect estrogen and progesterone receptors in cancer cells from a sample of tissue.[10]

HER2 is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer[9]



HER2 is the target of the monoclonal antibody trastuzumab (marketed as Herceptin). Trastuzumab is effective only in cancers where HER2 is over-expressed. One year of trastuzumab therapy is recommended for all patients with HER2-positive breast cancer who are also receiving chemotherapy.An important downstream effect of trastuzumab binding to HER2 is an increase in p27, a protein that halts cell proliferation.Another monoclonal antibody, Pertuzumab, which inhibits dimerisation of HER2 and HER3 receptors,

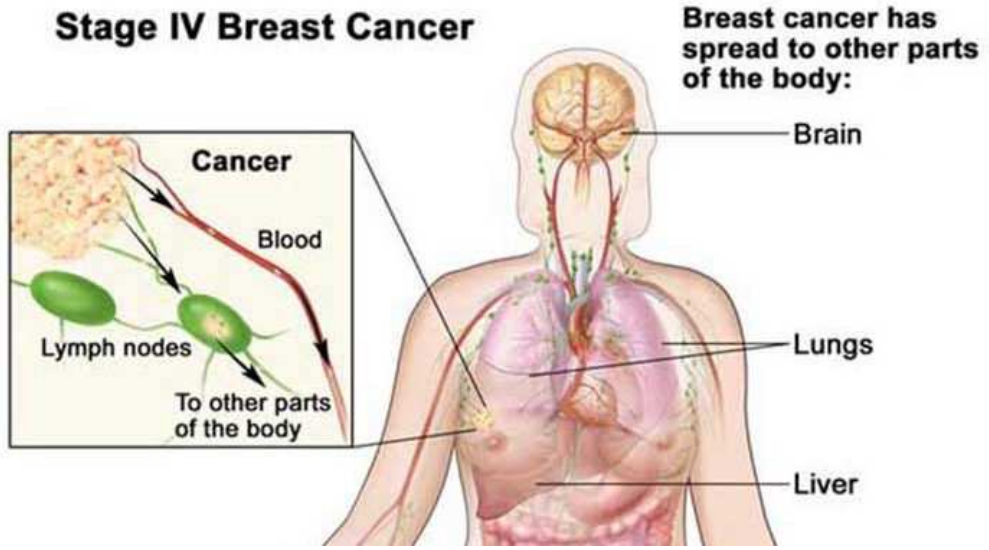
CLINICAL FEATURES:



Although any portion of the breast, including the axillary tail, may be involved, breast cancer is found most frequently in the upper outer quadrant.

- Hard lump, which may be associated with indrawingof the nipple.
- As the disease advances locally there may be skin involvement with peaud'orange or frankulceration and fixation to the chest wall. This is described as cancer-en-cuirasse when the disease progresses around the chest wall.
- Axillary lymphadenopathy

- Signs and symptoms of metastasis



1. Opposite axilla and opposite breast

2. Abdominal examination for secondaries in the liver whichpresent as nodular liver, ascites and Krukenberg'stumourbilateralbulky ovarian metastasis.

3. Rectal examination to rule out deposits in rectouterinepouch

4. Respiratory system examination to rule out effusion.

5. Bony tenderness should be looked for in the spine, longbones, skull, etc.

STAGING OF CARCINOMA BREAST:

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple not associated with invasive carcinoma or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin
T4a	Extension to the chest wall, not including only pectoralis muscle adherence or invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema of the skin
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN0(i–)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (IHC)
pN0(mol+)	Positive molecular findings (RT-PCR), but no metastasis detected by histology or IHC
pN1	Micrometastases; or metastases in one to three axillary nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm)
pN1a	Metastases in one to three axillary nodes; at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastasis or macrometastases detected by sentinel lymph node biopsy (not clinically detected)
pN1c	Metastases in one to three axillary nodes and in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in four to nine axillary nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in four to nine axillary nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ten or more axillary nodes; or in infraclavicular (level III axillary nodes); or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary nodes; or in more than three axillary lymph nodes and internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Breast cancer stage is done with physical examination, imaging studies (clinical staging) and on definitive surgical treatment by pathologic examination of the primary tumor and regional lymph nodes (pathologic staging).

TNM Staging Labels		
T (Tumor)	**N (Lymph Nodes)**	**M (Metastasis)**
T0: No evidence of tumor. Tis: Tumor hasn't grown into nearby tissue. T1 to T4: Tumor has grown into nearby tissue (numbers 1–4 describe how much the tumor has grown).	N0: No cancer found in lymph nodes. N1 to N3: Cancer has spread into lymph nodes (numbers 1–3 are based on how many nodes are involved and how much cancer is in them).	M0: Cancer hasn't spread to other parts of the body. M1: Cancer has spread to other parts of the body.

With the T, N and M values, you can use the below table to find your cancer stage.

Overall Stage	T	N	M
Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IIA	T0 T1 T2	N1 N1 N0	M0 M0 M0
Stage IIB	T2 T3	N1 N0	M0 M0
Stage IIIA	T0 T1 T2 T3 T3	N2 N2 N2 N1 N2	M0 M0 M0 M0 M0
Stage IIIB	T4	Any N	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Breast cancer is staged according to the TNM classification system, which groups patients into four stage groupings based on the size of the primary tumor (T), status of the regional lymph nodes (N), and presence or absence of distant metastasis (M). The most commonly used system is of American Joint Committee on Cancer (AJCC). This system is updated every 6 to 8 years to reflect current understanding of tumor behavior.

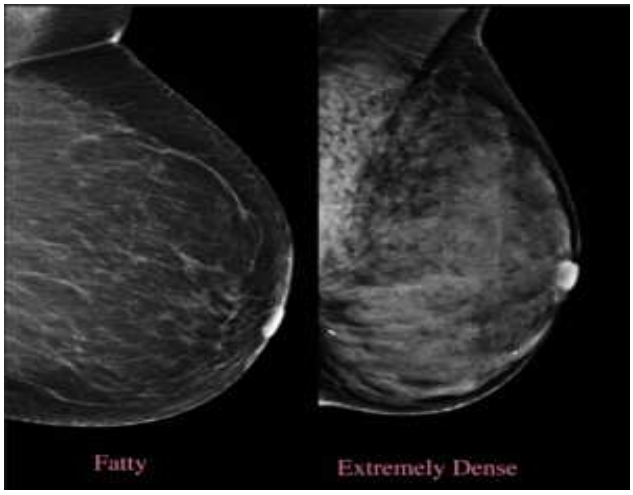
INVESTIGATIONS AND MANAGEMENT

BLOOD INVESTIGATIONS:

- Complete blood Count: Hb% may be decreased due to carcinoma/ anemia.
- Liver function test: increased ALP suggests bone or liver metastasis,
- D-dimer can be considered as a potential prognostic marker as shown in various studies.

INVESTIGATIONS FOR DIAGNOSIS:

- Mammogram and ultra sound of breast with axilla:



Normal Mammogram

Used as a Screening test forAsymptomatic women of more than 40 years.

Used as Diagnostic :Women with pain in the breast, mass,discharge, clinical features suggestive of malignancy.

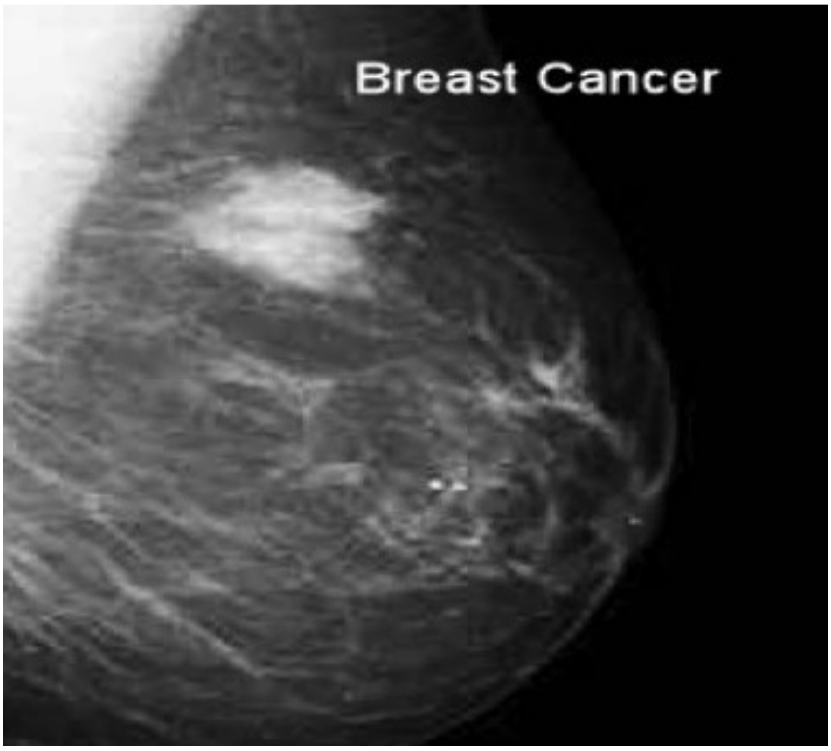
Mediolateral oblique view is for outer quadrant and axilla and Craniocaudal view is for medial quadrants. Radiation dose is 0.1 centigray (cGy).

Benign lesions like fibroadenoma shows round, punctate, popcorn like.

Mammogram-fibroadenoma

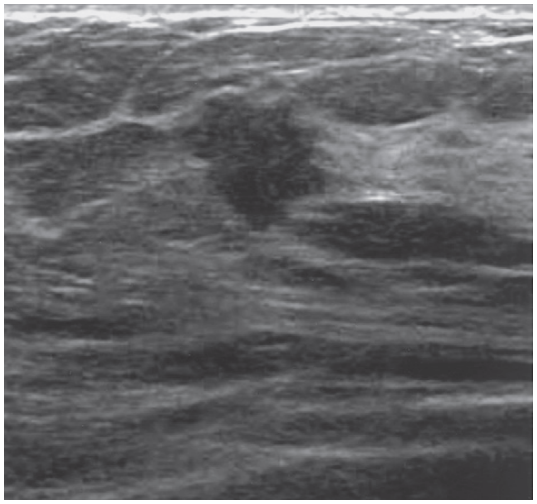
Highly suspicious—pleomorphic, heterogenous Solid mass with irregular edges speculation,Long tentacles—Tentaculation, Fine scattered calcification—Microcalcification, Distortion of architectural pattern of the breast.

Asymmetrical thickening of breast tissues.



Carcinoma breast Mammogram with irregular edges

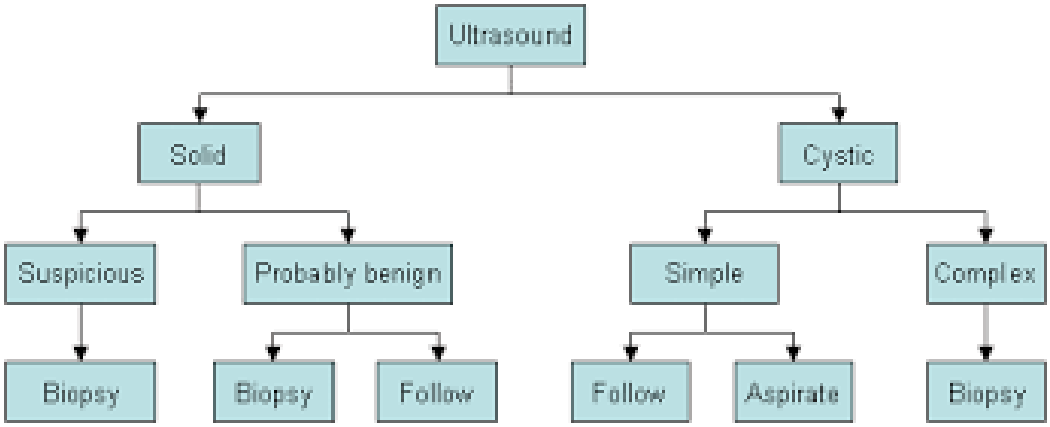
ULTRASOUND OF BILATERAL BREAST AND AXILLA:



Ultrasound image of breast cancer.

The mass is solid, contains internal echoes, and displays an irregular border. Most malignant lesions are taller than they are wide.

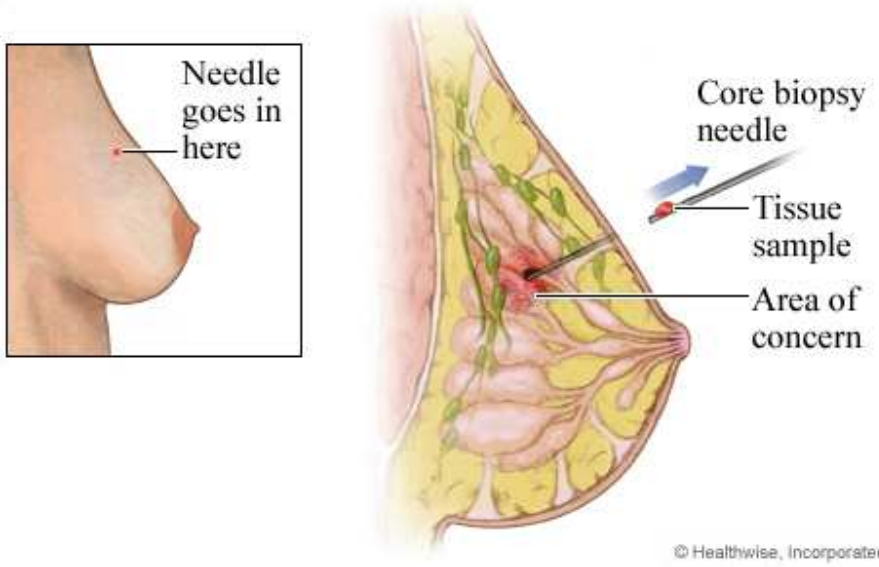
Ultrasonography is useful in determining whether a lesion detected by mammography is solid or cystic. Ultrasonography can be useful for discriminating lesions in the patient with dense breasts. However, it has not been found to be a useful screening tool because it is highly dependent on the operator performing the freehand screening and there is a lack of standardized screening protocols.



The American College of Radiology Imaging Network (ACRIN) has performed a trial (ACRIN 6666) inhigh-risk women in whom mammography and ultrasonographywere performed in randomized order to compare the sensitivity, specificity, and diagnostic yield of ultrasonography plus mammography compared with mammography alone.

Category	Assessment	Follow-up
0	Need additional imaging evaluation	Additional imaging needed before a category can be assigned
1	Negative	Continue annual screening mammography (for women over age 40)
2	Benign (noncancerous) finding	Continue annual screening mammography (for women over age 40)
3	Probably benign	Receive a 6-month follow-up mammogram
4	Suspicious abnormality	May require biopsy
5	Highly suggestive of (cancer)	Requires biopsy
6	Known biopsy – proven malignancy (cancer) <	Biopsy confirms presence of cancer before treatment begins

The investigators found that the combination of ultrasonography and mammography allowed for an increased diagnostic yield of 4.2cancers/1000 women. Ultra sonogram of the contralateral breast to rule out bilateral breast disease and ultra-sonogram of the axilla to rule out axillary lymphadenopathy.



Fine Needle Aspiration Cytology

Fine-needle aspiration (FNA) biopsy is a common tool used in the diagnosis of breast masses. It can be done with a 22-gaugeneedle, an appropriate-sized syringe, and an alcohol preparationpad. The aspirate must be properly prepared on a slide for cytologicexamination to be clinically useful. The main usefulness ofFNAC is differentiation of solid from cystic masses, but itmay be performed whenever a new, dominant, unexplained massis found in the breast.

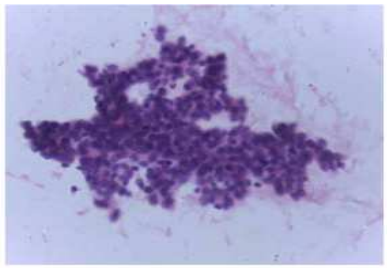


Fig.1: FNAC showing clusters of benign ductal cells (x 40).

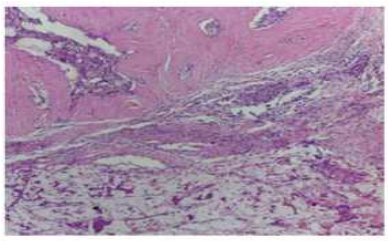


Fig.2: Histologic section showing fibroadenoma (arrow) and invasive mucinous carcinoma (double arrow) (H & E, x 10).

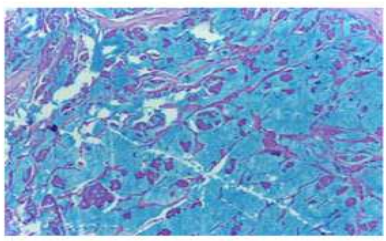


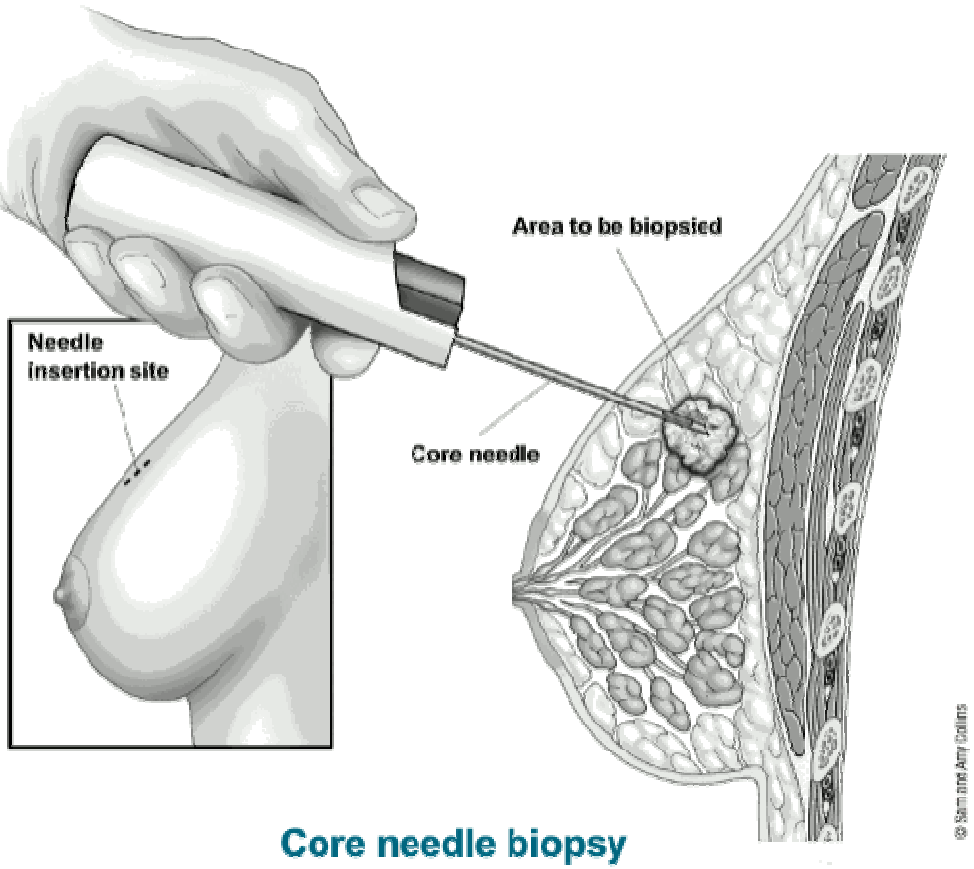
Fig.3: Clusters of well differentiated tumor cells floating in sea of extracellular mucin (Alcian blue stain, x10).

Most clinicians recommend core needle biopsy for definitive histologic diagnosis prior to surgical intervention.

A positive result on FNA biopsy allows the surgeon to begin informed discussions with the patient; however, definite plans for treatment should be based on the histologic diagnosis from a Core Needle Biopsy.

- CORE NEEDLE BIOSPY

  This technique is preferred for the diagnosis of palpable lesions, as core needle biopsy provides hormonal status of the tumor, for treatment of the disease.



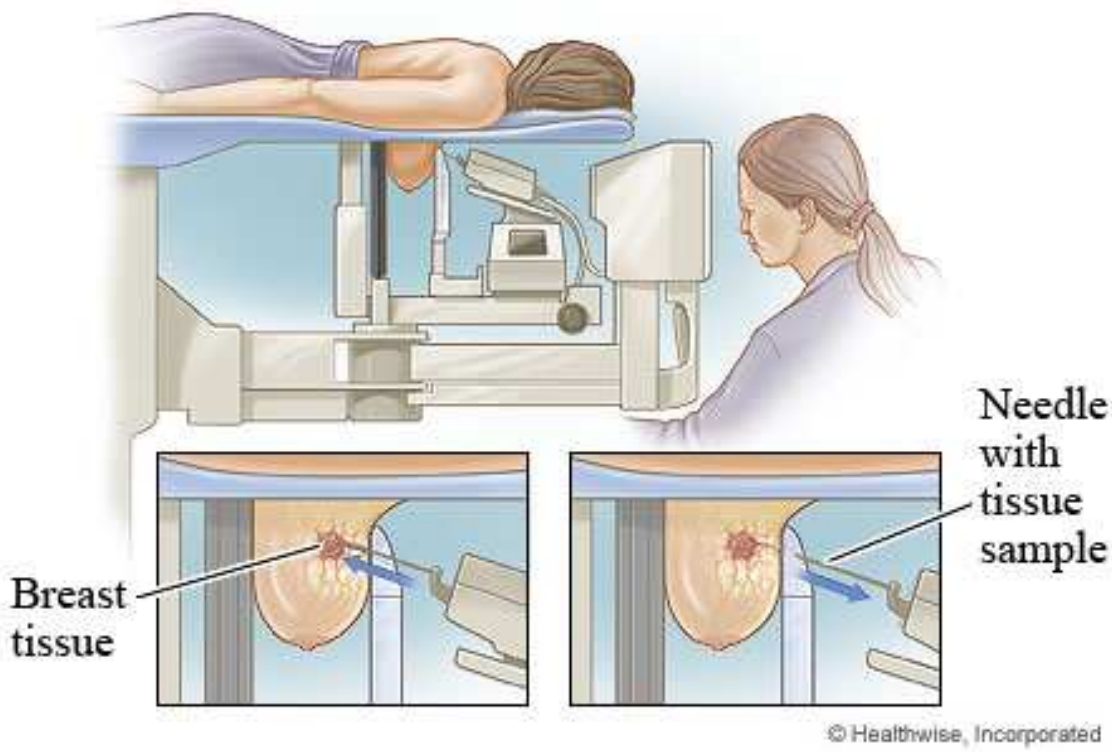
In case of non- palpable lesions:

Biopsy can be performed under mammographic (stereotactic), Ultrasonography guidance, or Magnetic resonance imaging (MRI) guidance.

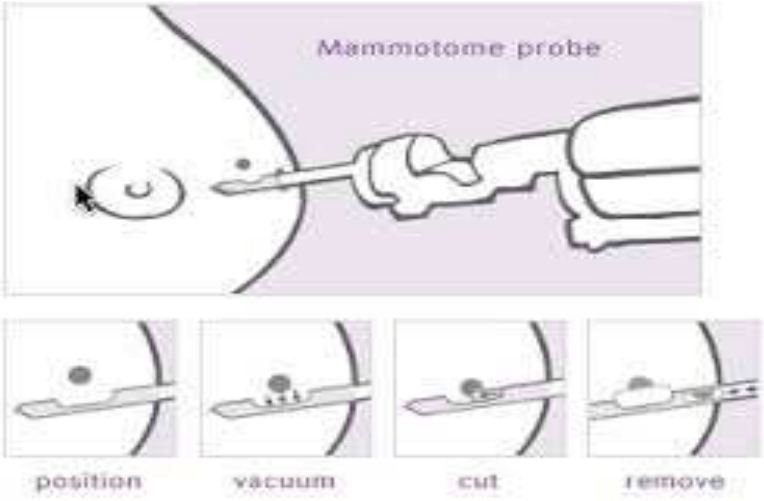
Mass lesions that are visualized on ultrasonography can be sampled under ultrasonography guidance; calcifications and densities that are best seen on mammography are sampled under stereotactic guidance.

During stereotactic core needle biopsy, the breast is compressed, most often with the patient lying prone on the stereotactic core biopsy table.

A robotic arm and biopsy device are positioned by computed analysis of triangulated mammographic images. After local anesthetic is injected, a small skin incision is made and an 11-gauge core biopsy needle is inserted into the lesion to obtain the tissue sample.

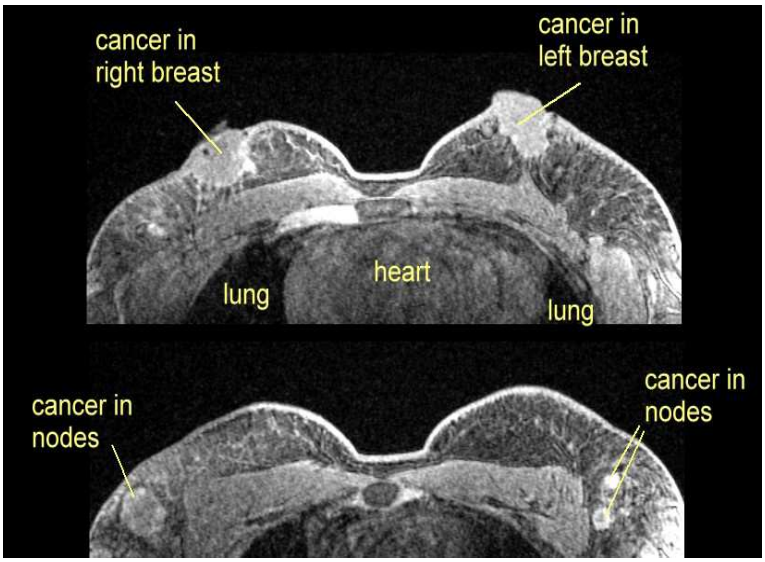

Needle with tissue sample
Breast tissue
© Healthwise, Incorporated

Mammotome:


Mammotome probe
position
vacuum
cut
remove

It is a hand held vacuum-assisted biopsy instrument which can be used under image (ultrasound or stereotactic) guidance. It gives accurate diagnosis of no palpable mammographic abnormalities.

Role of MRI in Carcinoma Breast:



• Particularly useful in detecting malignancy when mammographically subtle or occult (lobular carcinoma).

• It can differentiate scar tissue from cancer. Hence can detect local recurrence after surgery.

• MRI is better than mammogram in assessing the response of the tumour to neoadjuvant chemotherapy.

• It is also better investigation in dense breasts and in pregnancy.

• Also for imaging of the breast with implants.

Unknown primary with axillary nodes are positive for adenocarcinoma. MRI is the ideal investigation to detect a impalpable breast lump.

‘TRIPLE ASSESSMENT’

• History and clinical examination

• Imaging : Ultrasound/Mammogram

• Fine Needle Aspiration Cytology/Core Needle Biopsy

Early Breast Carcinoma EBC (Stage I and Stage II) Staging work up:

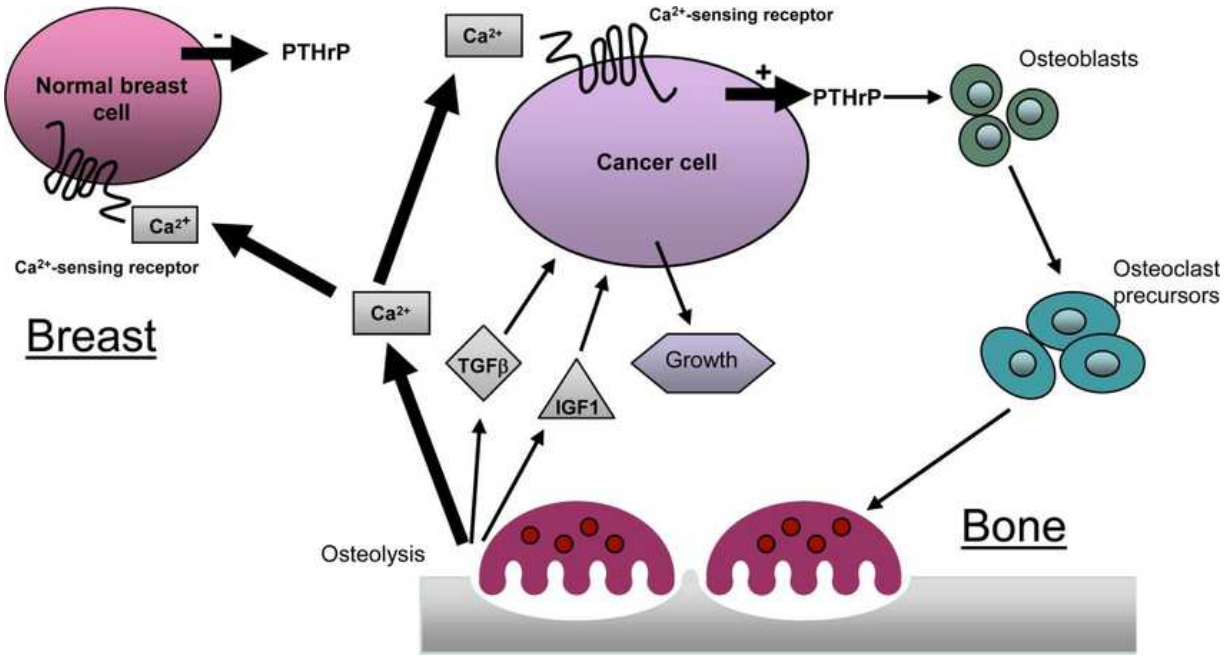
- Chest X-ray: Rule out pulmonary secondaries/ pleural effusion

  - Cannon ball type :Presents late

  - Lymphangiectatictype: Presentswith intractable cough.

- Abdominal ultrasonography done to rule out liver metastasis, hepatomegaly, ascites, rectovaginal deposits.
- Xray of long bones, whole spine with pelvis, cranium: to rule out bone metastasis.

Locally Advanced Breast Carcinoma and Advanced Breast Carcinoma (Stage III and Stage IV)



- Contrast Enhanced Computer Tomography Chest(CECT chest) to rule out lung metastasis, pleural effusion, mediastinal widening.
- Contrast Enhanced Computer Tomography Abdomen and pelvis: to rule out liver metastasis, ascites, rectal deposits, as the stage of the tumor increases there is increased incidence of systemic metastasis which cannot be picked up by Xrays of chest and long bones, whole spine and cranium and USG Abdomen and pelvis
- Bone scan: rule out bone metastasis
- Treatment of early breast cancer—Stage I, IIA

A. Primary

• Locoregional control of primary disease is by surgery in the form of Modified radical mastectomy (MRM) or Breast conservative surgery (BCS).

B. Adjuvant

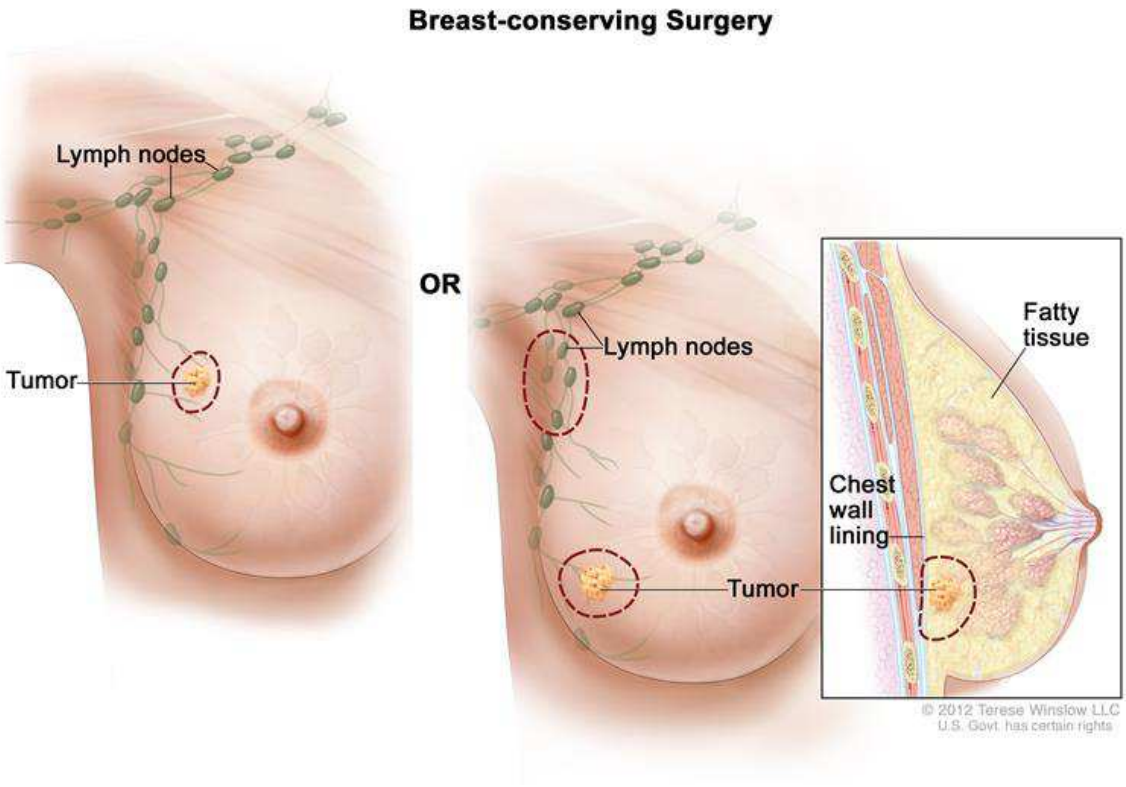
• Loco regional control of residual disease is by radiotherapy

• Systemic control of disease is by Hormonal therapy or Chemotherapy.

SURGERY:

1. Wide local excision (lumpectomy) is indicated in tumorsless than 4 cm in size and with well differentiated histology. It includes removal of the tumor with a rim of at least 1 cm of normal breast tissue. If the nodes are palpable and enlarged, this is combined with axillary block dissection, using separate incision. Currently, this procedure has become more popular. It is also called as Breast Conservative Surgery. Radiotherapy to the breast tissue is mandatory in all cases of breast conservation surgery.

BREAST CONSERVATIVE SURGERY:



• Involves the following three steps apart from removal of cancer alone:

1. Removal of tumor with wide margin

2. Adjuvant radiotherapy

3. With or without assessment of axillary lymph node status.

Indications:

• Solitary cancer

• Possible to excise the tumor with tumor free margins without disrupting the breast cosmetically

• No contraindications to RT (e.g. pregnancy, collagen vascular disorders which may exaggerate the reaction and prior RT to same breast)

• Well motivated patient.

Contraindications:

• Presence of two or more primary tumors in separate areas of breast

• Diffuse malignant appearing calcification

• History of prior radiation to breast (will be a contraindication for full breast radiation)

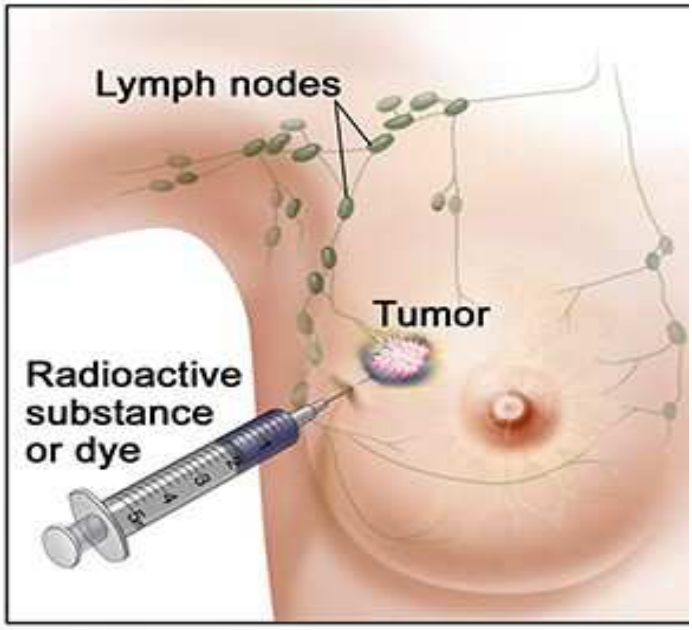
• Pregnancy (1st and 2nd trimester) can be done in third trimester.

• Collagen vascular disorders where RT cannot be given (RT exaggerates the disorder)

• Large tumor in a small breast that does not respond to induction chemotherapy

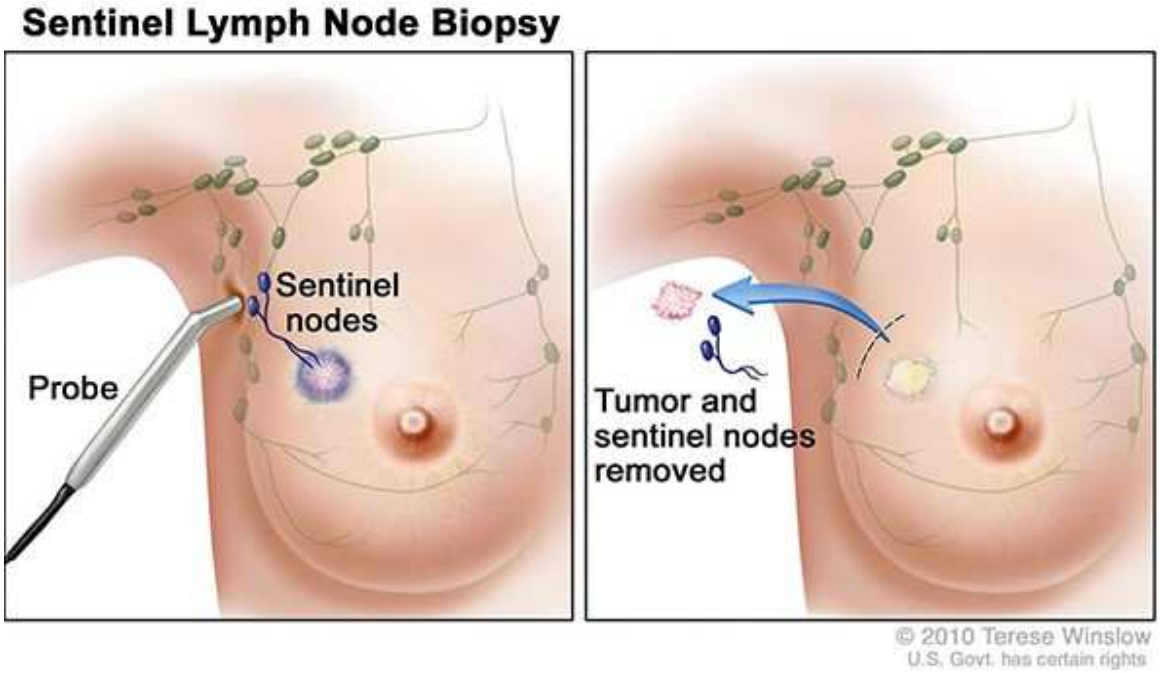
SENTINEL NODE BIOPSY

Sentinel node: 1st node to drain the tumor.



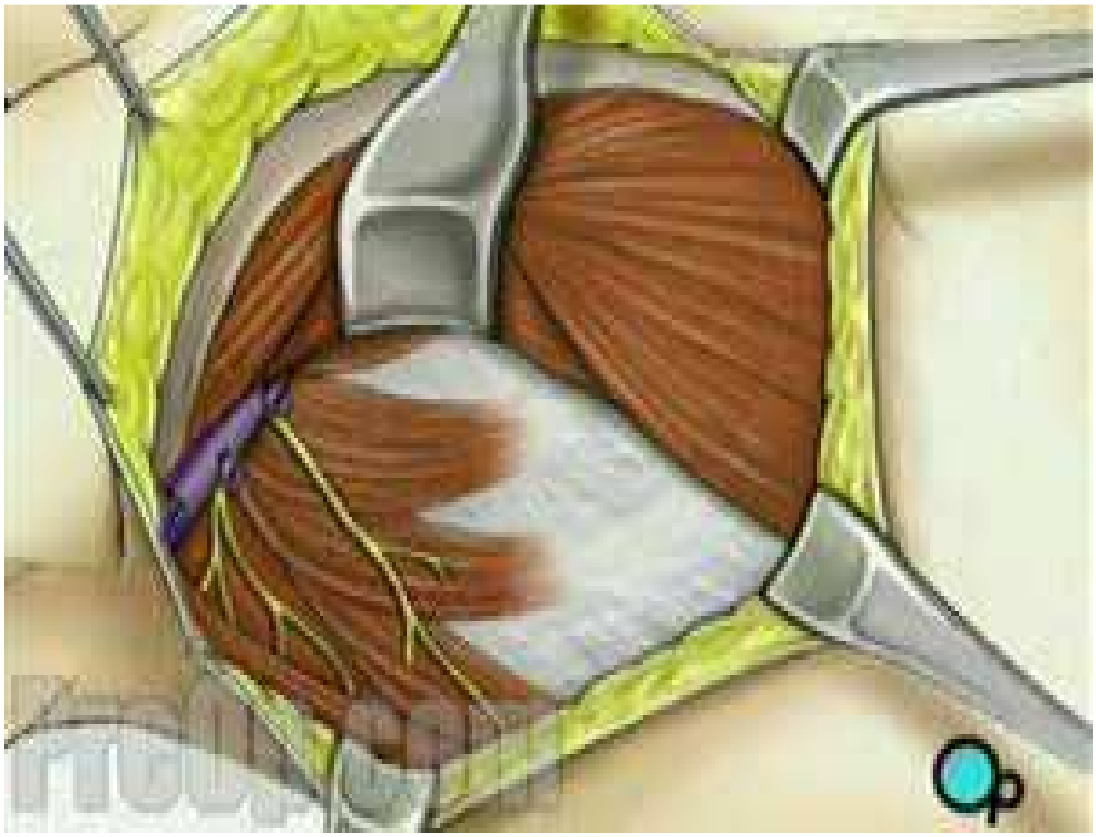
Two methods:

- On the day prior to surgery, the radioactive colloid (Technetium 99m sulfur or radioalbumin) is injected using a tuberculin syringe into three to four separate sites at the cancer area or subdermally proximal to cancer; the node biopsied using hand-held gamma camera peroperatively.



During surgery patent blue dye (methylene blue) is injected into the tumor and the sentinel node identified and sent for frozen section biopsy.

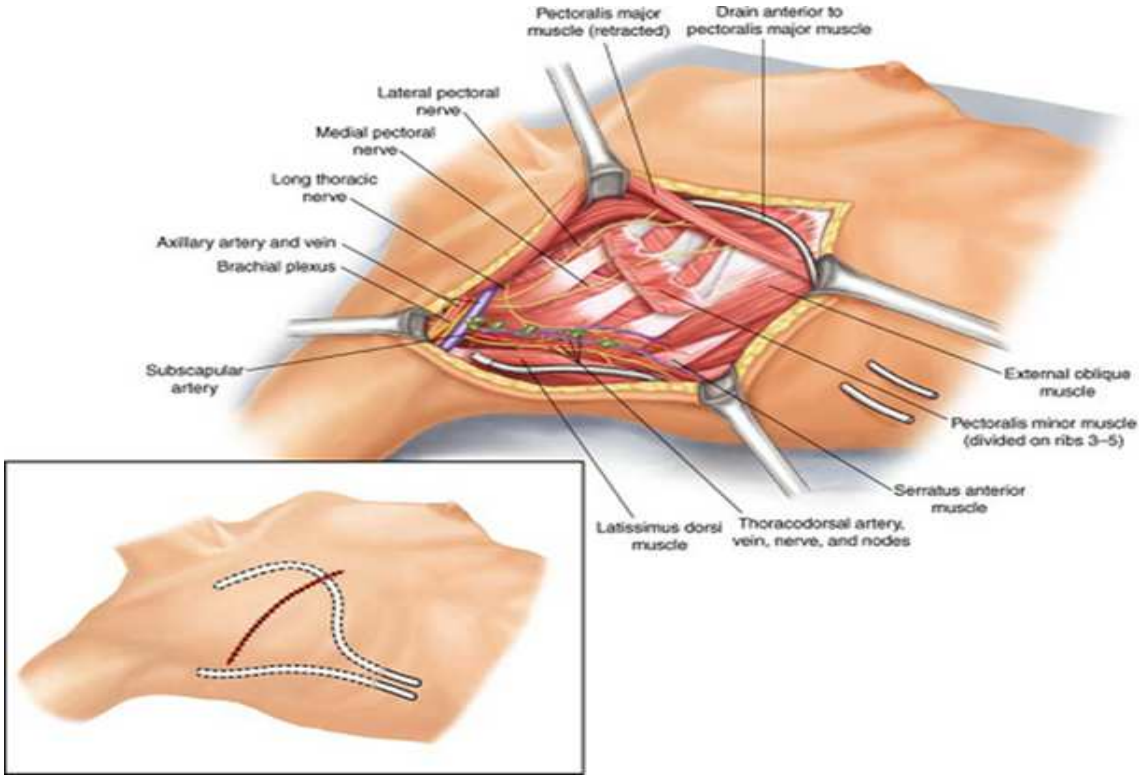
If sentinel node biopsy is positive for malignancy, can procedure with axillary node dissection with separate axillary incision, followed by radiotherapy.2.Modified Radical Mastectomy (MRM) is equally good (good retraction of pectoralis minorfacilitates axillary dissection - Auchincloss modification.



Advantages of Modified Radical Mastectomy over Halsted radical mastectomy:

• Cosmetically better accepted as axillary fold is maintained.

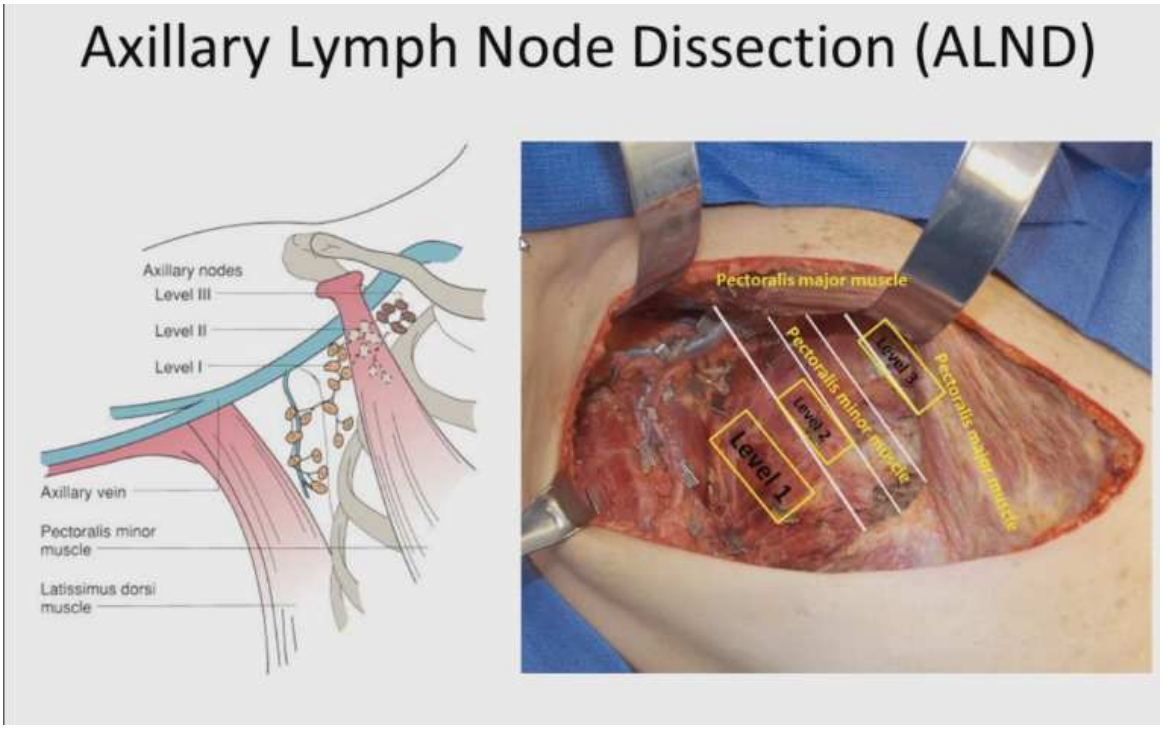
• Function of the shoulder is better, and it gives a stronger and more useful arm.



Patey mastectomy: It is also a type of modified radical mastectomy. In this, the entire breast including nipple and areola (simple mastectomy) are removed with, pectoralis minor, followed by axillary block dissection. A complete axillary block dissection should include node clearance up to Level III.

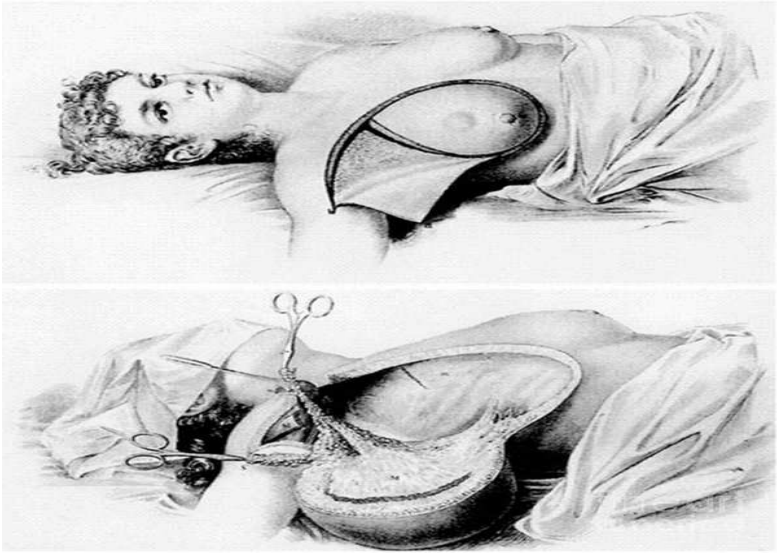
Scanlon's operation: Is a modified Patey'soperation wherein instead of removing pectoralisminor, it is incised to approach the affected Level III lymph nodes

AXILLARY NODE DISSECTION:



Right axillary clearance: (a)The lateral border of pectoralis major is defined and the fascia incised along its length to gain access into the axilla. (b) The axillary contents are retracted downwards and the fat over the axillary vein is carefully incised until it can be identified. (c) The apical division of fat and lymphatics is easier after the medial and posterior wall dissection has been completed.

Radical mastectomy:



In this operation, following structures are removed

• Entire breast including nipple and areola, skin overlyingthe tumour along with fat, fascia and lymphatics.

• Axillary block dissection, including complete clearance of axillary fat and up to Level III nodes clearance.

• Sternocostal portion of pectoralis major, entire pectoralisminor, few fibres and aponeurosis of internal oblique, serratus anterior, latissimusdorsi and subscapularis.

Three important structures should be preserved

• Axillary vein

• Bell's nerve (long thoracic nerve which supplies serratusanterior)

• Cephalic vein.

Disadvantages of radical mastectomy

• Mutilating surgery

• Poor cosmetic results

• Lymphoedema of arm

• High morbidity rate

Modified radical mastectomy is more frequently done.

In our study we proceeded with Modified Radical Mastectomy-Auchincloss method for operable carcinoma.

Adjuvant treatment—2 types

A. Radiotherapy

• Following either MRM or BCS, the residual disease is controlled by administering radiotherapy in a dose of 4.500-5,000 cGy to the breast over 5-6 weeks.

• In the absence of nodal involvement axilla may be spared radiation

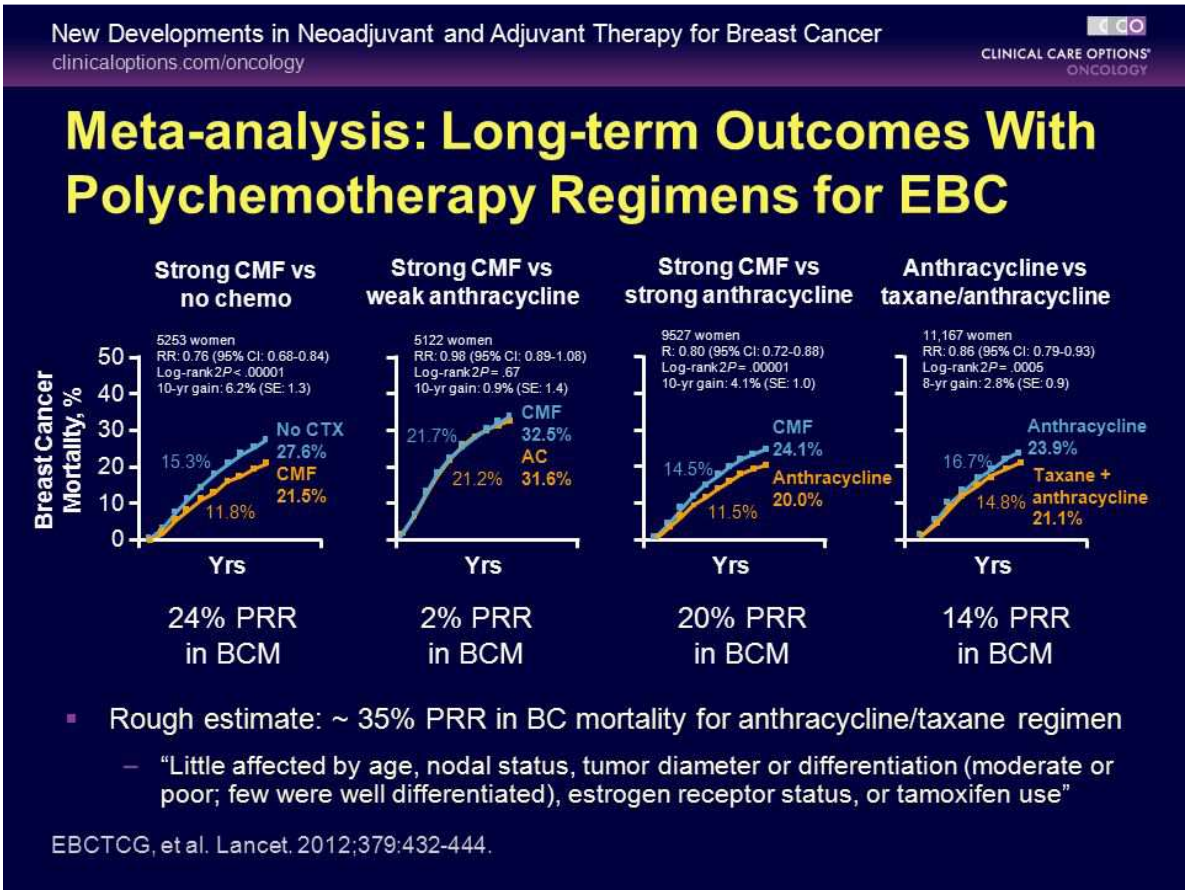
• If 4 or more nodes are involved, then the field of radiation should include supraclavicular and internal mammary chains.

INDICATIONS FOR POSTOPERATIVE RADIOTHERAPY

- Tumor margin is positive
- Pectoralis major is involved
- Inner quadrant tumor
- High grade tumors
- Axillary clearance not satisfactory
- Breast conservative surgery
- Tumor size more than 5 cm

B. Systemic therapy:

I. Adjuvant chemotherapy



It should be considered in all cases of early breast cancerirrespective of menopausal status, hormone receptor status and nodal status.

• 1st line agents: Cyclophosphamide, Adriamycin, 5-Fluorouracil (CAF). Because of cardiotoxicity of adriamycin, epirubicin is preferred as in FEC regimen.

The preferred regime is anthracyclines (adriamycin) which have a better response rate. Either CAF or FEC every 21 days x 6 cycles or at every 21 days x 4 cycles or just Adriamycin with cyclophosphamide (AC). However; the CMF (Cyclophosphamide, Mitomycin, Fluorouracil) regimen still continues to be used widely due to economicalreasons.

• 2nd line agents: Taxanes—Paclitaxel and Docetaxel

• 3rd line: Gemcitabine

Indication for adjuvant chemotherapy

• Tumor> 1 cm

• Tumor< 1 cm with ER -ve, HER-2 +ve, high grade.

Adjuvant trastuzumab therapy:

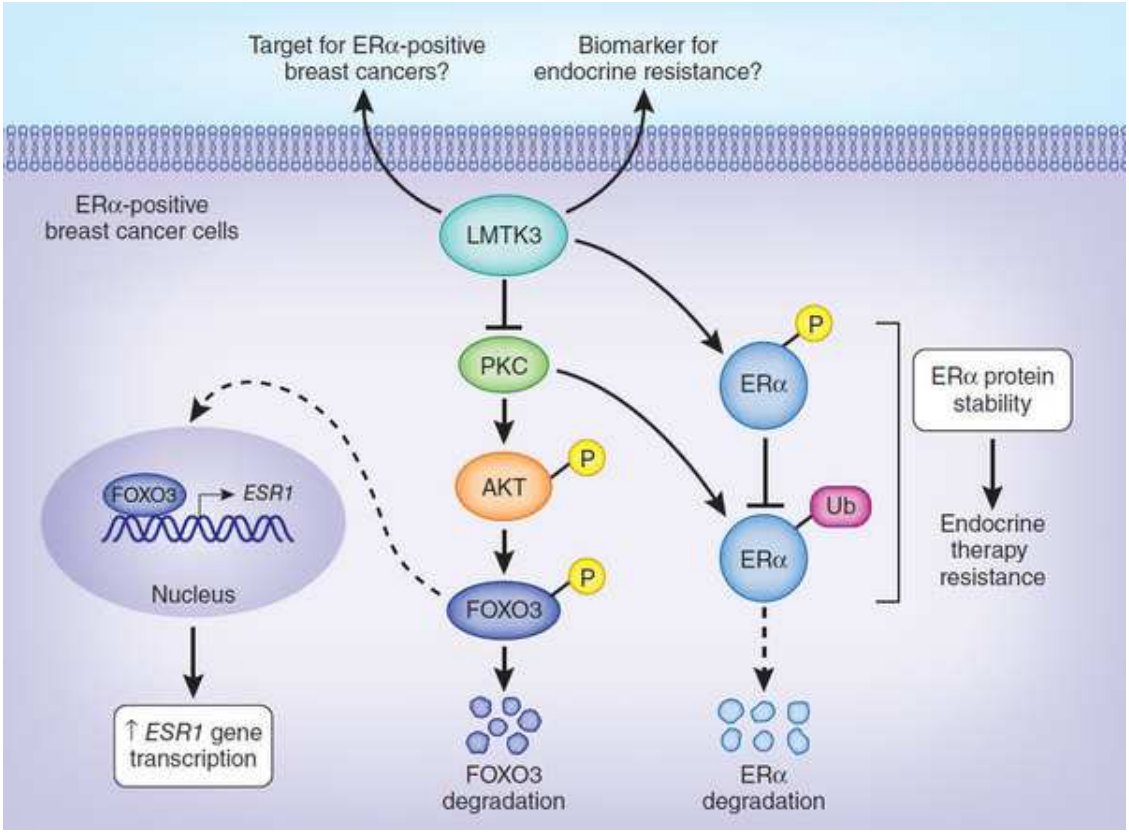
Trastuzumab: A monoclonal antibody against tyrosine kinasereceptor (HER-2 receptor) is administered in patients with HER-2 +ve patients since it has been shown to improve disease free survival (DFS) by 50%, when it is combined with taxane-based chemotherapy. It potentiates effects of chemotherapy.

Dose: Loading 4 mg/kg.

Maintenance 2 mg/kg/ week for 1 year.

II. Adjuvant hormonal therapy

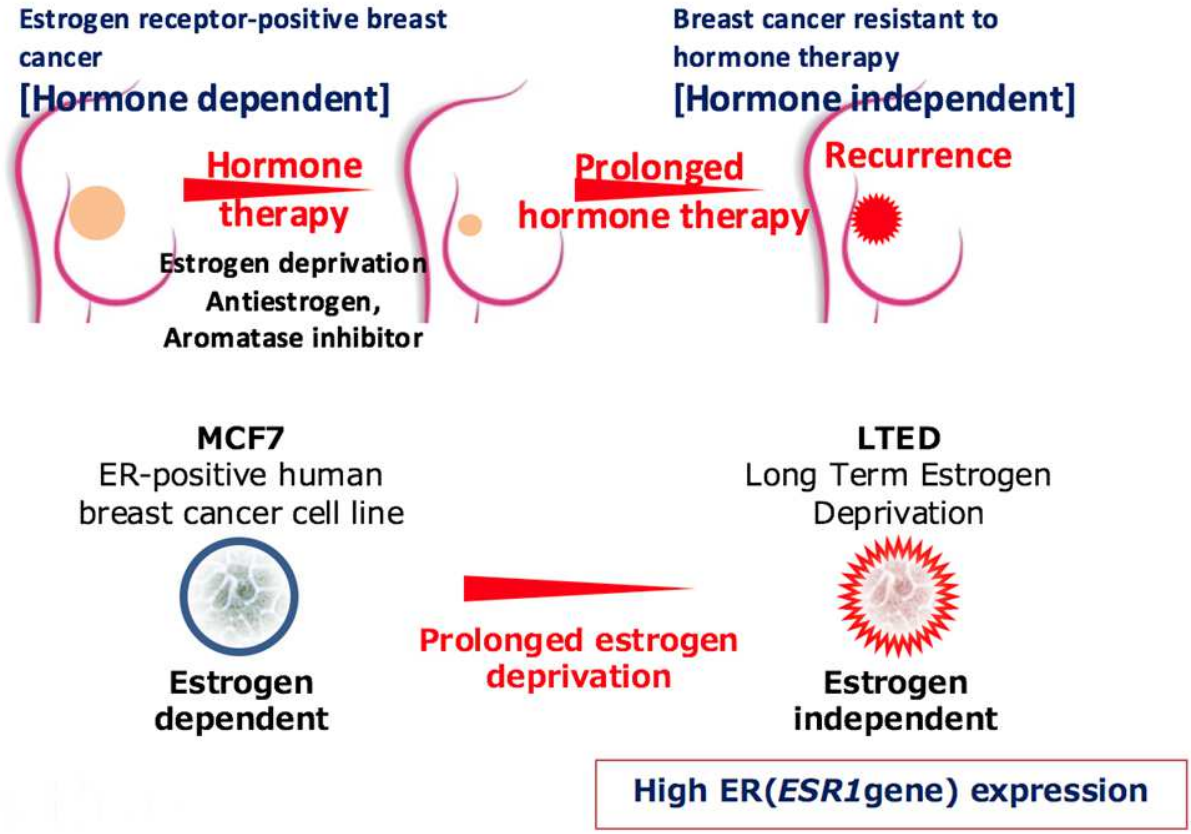
Hormonal therapy is administered to patient in whom the tumor expressed steroid hormone receptors, i.e. ER/ PR.Those who are negative for ER/PR,will not benefit from these drugs.



The drugs are categorized as follows

• 1st line—Anti-oestrogens—Tamoxifen.Commonly, Tamoxifen in a dose of 20 mg is used for 5 years, to be started only after completion of chemotherapy.

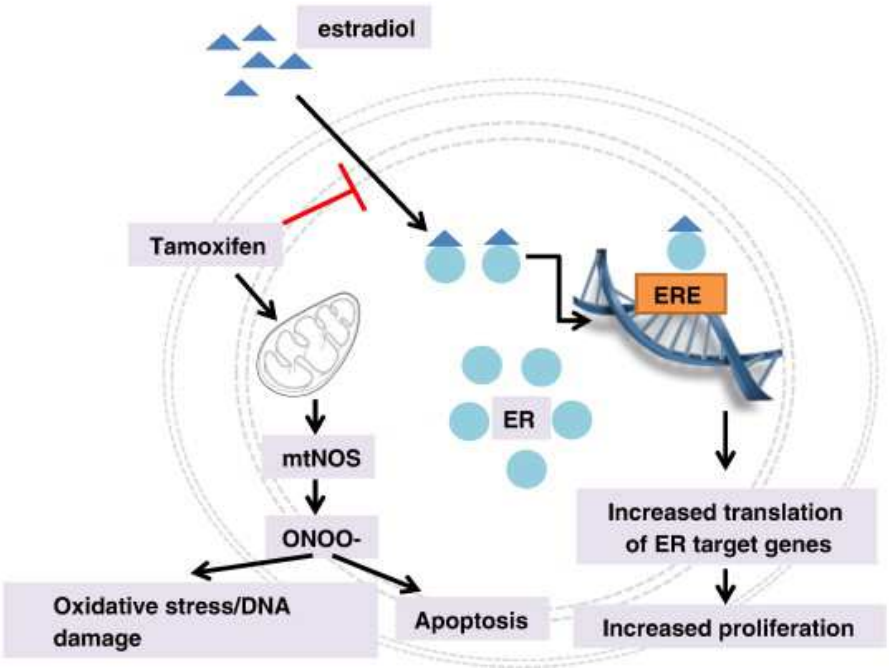
• Raloxifene is an oral selective estrogen receptor modulator (SERM) that has oestrogenic actions on bone and antioestrogen actions on the uterus and breast. It is used in the prevention of osteoporosis in postmenopausal women. Studies have proved that no specific advantage of raloxifene in the adjuvant treatment of breast cancer rather than established drugs such as tamoxifen.



• 2nd line—Aromatose inhibitors. They prevent synthesis of endogenous oestrogens/steroids by blocking the aromatase enzyme which converts androstenedione to oestradiol in the adrenals.

They are: 1st generation:Aminoglutethimide and 2nd generation—Anastrozole, Letrozole, Exemestane given to postmenopausal patients.

• Letrozole costlier than tamoxifen, reduces oestrogen levels by 98%, thus slows down oestrogen sensitive breast cancers.lt is given in the dose of 2.5 mg per day. Side effects:include vaginal bleeding, vaginal dryness, night sweats, hot flushes, osteoporosis, etc. Aromatase inhibitor in sequential use after Tamoxifen for a further period of 5 years has been shown to be beneficial.



• 3rd line—Progestogens—Megestrol acetate 400 mg per day can be given

• 4th line—Androgens such as Fluoxymestrone in the dose of 30 mg daily is another drug (Last 2 drugs are rarely given).

REVIEW OF LITERATURE

4.D-DIMER WITH OPERABLE CARCINOMA BREAST: REVIEW OF LITERATURE

D-dimer, a biomarker of the fibrinolytic system is elevated in carcinoma patients as found in various studies. In our study pre-operative plasma d-dimer is evaluated by

Particle Enhanced Imunoturbidimetry method, with biological reference interval

Less than 0.5 ugm FEU/ml: negative

More than 0.5 ugm FEU/ml: positive

-LiW et al(2018) karger journal studied Prognostic role of pretreatment plasma d-dimer in patients with solid tumors, a systemic review and meta- analysis and concluded that there was strong evidence of elevated pre-treatment D-dimer associated with unfavorable overall survival and stages of the tumor.[11]

-Cihan et al(2012) , in their study High D-dimer are associated with poor prognosis in cancer patients, concluded that higher d-dimer levels are associated with poor poorover all survival and increased mortality risk in cancer patients.[6]

-In bhavesh et al study showed statistically significant relationship between d-dimer according to lymphovascular invasion and increase in tumor size, such that d-dimer has a possible role as prognostic factor in carcinoma breast.[12]

-In ganpat et al study showed significant correlation between mean values of plasma d-dimer, tumor size, lymphovascular invasion, histological grade, advancing stage of the disease.[13]

-In hudhaifah shaker et al study, plasma d-dimer correlated with lmphovasuclar invasion and tumor size statistically significant but not significant with hormone receptor status.[14]

-In Blackwell et al study concluded a linear regression modeling showed relationship between the presence of lymphovascular invasion and elevated d-dimer levels.[15]

-In Rajendran et al study showed statistically significant relationship between values of d-dimer and lymphovascular invasion, number of nodes involved and advancing stage of carcinoma breast. No significance between d-dimer and increasing tumor size.[16]

-In L.Y Dirix et al study, Plasma fibrin D-dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer.

Concluded that significant increased d-dimer levels as a predictor for rapid tumor growth, shorter survival in breast cancer patients.[6]

-S, H., Sringeri et al (2018) in their study showed that plasma D-Dimer levels were elevated in breast carcinoma patients. Increased D-Dimer levels are an important marker of clinical stage, lymphovascular invasion, lymph node involvement, and tumor metastasis.[17]

-sapnapatel et al (2018) concluded that study showed that high plasma D-dimer levels can be used as a marker for lymph node involvement and higher histopathological grade. Due to the ease with which plasma D-dimer levels can be obtained and its cost effectiveness, quantitative D-dimer levels can be added as addition blood investigation for carcinoma breast patients[18].

-Malik Zeb Khan et al, in their study Fibrinogen degradation products and d-dimer in patients with breast carcinoma, concluded The levels of Fibrinogen Degradation Products and D-Dimers are elevated in breast carcinoma, especially in those with distant metastasis[19].

-Khangarot, Shyamveer Singh et al (2011) studied Correlation of D dimer and factor VIII levels with histopathology in patients with breast carcinoma and concluded that D-dimer and factor VIII may be used as yardstick for systemic adjuvant therapy in node negative < 1 cm breast cancer. D-dimer can be prove to

be a convenient, safe and easily available biomarker which can be combined with conventional sentinel node biopsy in clinically node negative breast cancer to assess metastatic disease in axilla and reduce false negative results[20].

A DESCRIPTIVE STUDY OF:

ANALYTICAL STUDY OF

CORRELATION BETWEEN PLASMA

D-DIMER LEVELS AND

LYMPHOVASCULAR

INVOLVEMENT IN OPERABLE

CARCINOMA BREAST

5. MATERIALS AND METHOD

STUDY DESIGN:

Descriptive study

PLACE OF STUDY:

Department of general surgery –Govt.Stanley medical college &hospital

STUDY PERIOD: 8MONTHS

february2018 to September 2018.

PATIENT SELECTION:

The patients admitted to the Stanley Hospital in Department of General Surgery with FNAC/TRUCUT proven operable carcinoma breast during the study period.

INCLUSION CRITERIA:

FNAC/Trucut proven carcinoma breast.

EXCLUSION CRITERIA:

Other malignancies

Coagulation and bleeding disorders

Co-morbidities like myocardial infarction, cerebral vascular disease

Bilateral breast carcinoma

Recurrent breast carcinoma

SAMPLE SIZE: 90Patients

METHODOLOGY:

- Ethical committee clearance

- Informed consent

- Pre-operative plasma D-dimer levels will be analyzed in operable Carcinoma Breast Pre operatively and TNM Staging will be done according to American Joint Committee on Cancer(AJCC).Modified radical mastectomy done for the following patients.

Post operative HPE report for lymphovascular invasion, Stage of carcinoma breast compared to d-dimer levels.

D-DIMER: Normal range<0.5ug FEU/ml

During the study period out of 95 cases operated.90 cases taken for study purpose. Rest of the five cases did not come for reviewwith the histopathology report.Hence excluded from the study.

6.OBSERVATION AND RESULTS

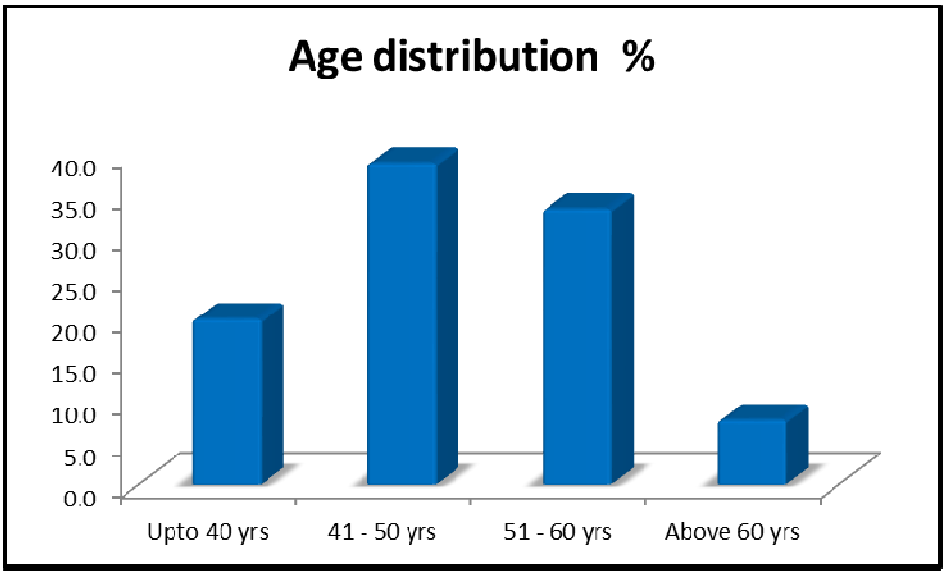
STASTISTICAL ANALYSIS

The collected data were analysed with IBM.SPSS statistics software 23.0 Version.To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significance between the bivariate samples in Independent groups the Unpaired sample t-test was used. For the multivariate analysis the KruskalWalli's test followed by the Mann-Whitney U test was used.To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value .05 is considered as significant level.

AGE

		Frequency	Percent
Valid	Upto 40 yrs	18	20.0
	41 - 50 yrs	35	38.9
	51 - 60 yrs	30	33.3
	Above 60 yrs	7	7.8
	Total	90	100.0

In our study out of 90 patients occurrence of carcinoma breast upto 40yrs was 18 patients(20%), 41-50 years of age- 35patients(38.9%), 51-60years of age-30 patients(33.3%), above 60years- 7patients(7.8%).

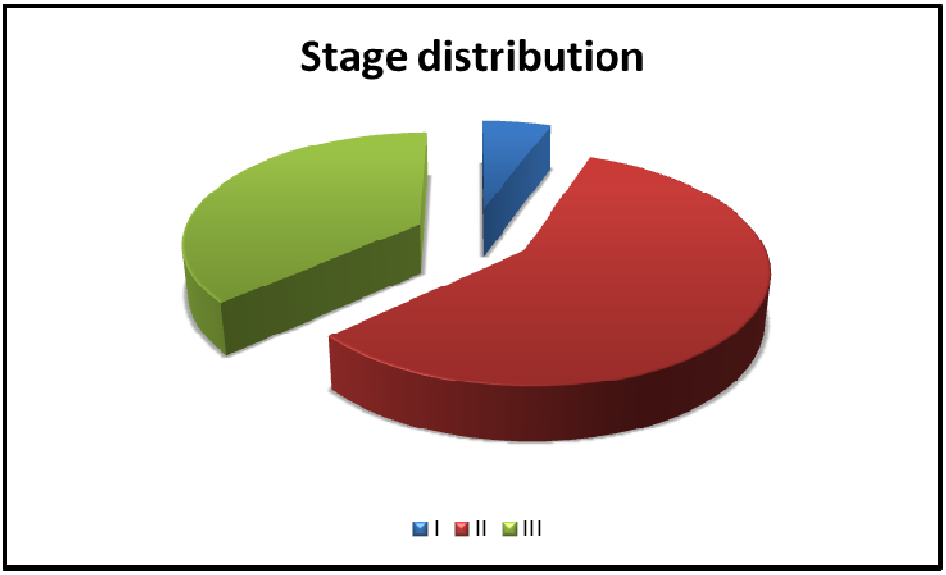


STAGE OF CARCINOMA BREAST:

Stage

		Frequency	Percent
Valid	I	5	5.6
	II	52	57.8
	III	33	36.7
	Total	90	100.0

In our study out of 90 patients, stage I – 5patients (5.6%), stage II- 52 patients (57.8%), stage III- 33 patients (36.7%).

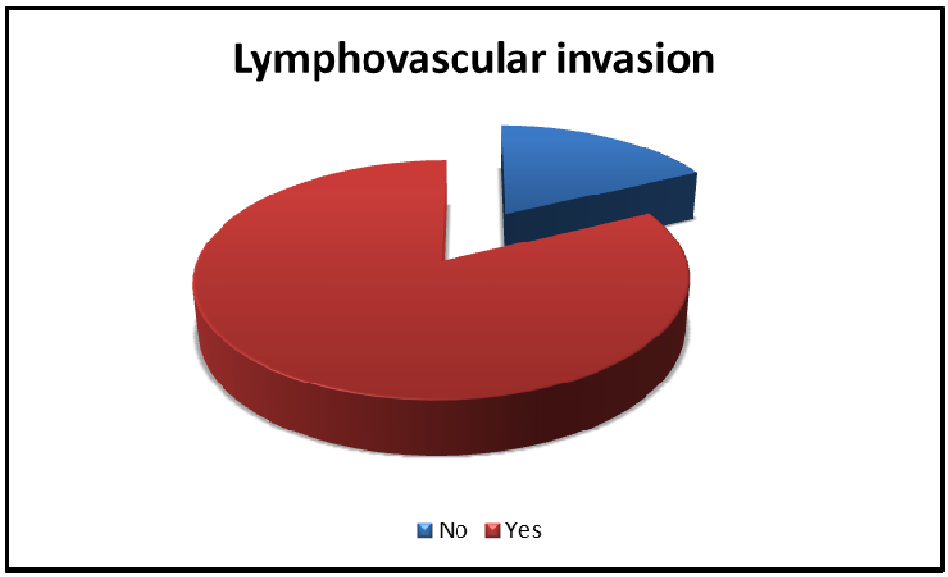


LYMPHOVASCULAR INVASION:

lymphovascular invasion

		Frequency	Percent
Valid	No	16	17.8
	Yes	74	82.2
	Total	90	100.0

In our study out of 90 operable carcinoma breast patients, post-operative Modified Radical Mastectomy histopathology report showed 74 patients with lymphovascular invasion present(82.2%), 16 patients with no lymphovascular invasion(17.8%).



Descriptives:

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age	90	35	75	49.41	8.399
d-dimer	90	.10	1.24	.5678	.25568
Valid N (listwise)	90				

Ranks

Stage		N	Mean Rank
d-dimer	1	5	18.80
	2	52	42.36
	3	33	54.50
	Total	90	

Descriptives

d-dimer

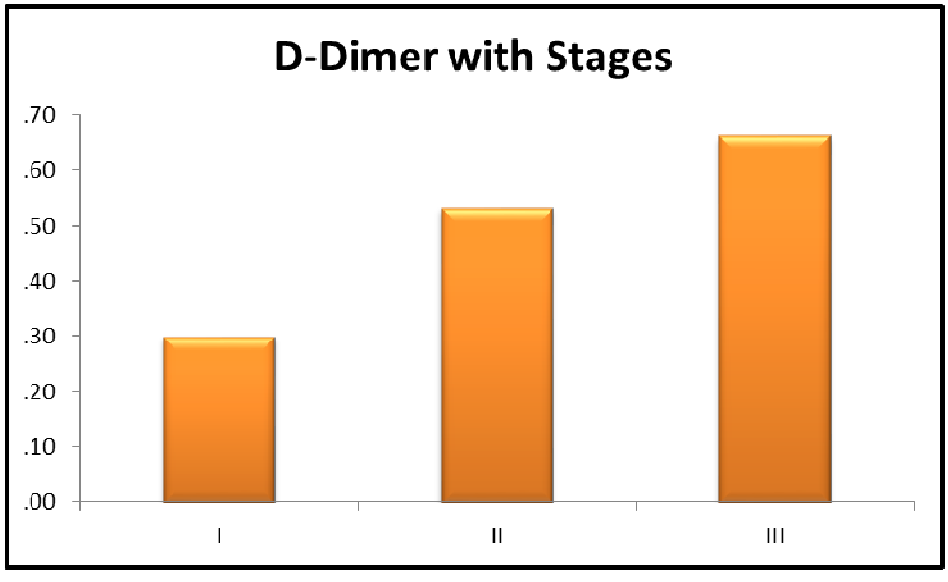
	N	Mean	Std. Deviation	Minimum	Maximum
I	5	.30	.16	.10	.50
II	52	.53	.24	.20	.90
III	33	.66	.25	.22	1.24
Total	90	.57	.26	.10	1.24

Test Statistics[a,b]

	d-dimer
Chi-Square	9.920
Df	2
Asymp. Sig.	.007

a. Kruskal Wallis Test

b. Grouping Variable: Stage



Ranks

Stage		N	Mean Rank	Sum of Ranks
d-dimer	1	5	15.20	76.00
	2	52	30.33	1577.00
	Total	57		

Test Statistics[a]

	d-dimer
Mann-Whitney U	61.000
Wilcoxon W	76.000
Z	-1.951
Asymp. Sig. (2-tailed)	.051
Exact Sig. [2*(1-tailed Sig.)]	.051[b]

a. Grouping Variable: Stage

b. Not corrected for ties.

Mann-Whitney Test

Ranks

Stage		N	Mean Rank	Sum of Ranks
d-dimer	1	5	6.60	33.00
	3	33	21.45	708.00
	Total	38		

Test Statistics[a]

	d-dimer
Mann-Whitney U	18.000
Wilcoxon W	33.000
Z	-2.790
Asymp. Sig. (2-tailed)	.005
Exact Sig. [2*(1-tailed Sig.)]	.003[b]

a. Grouping Variable: Stage

b. Not corrected for ties.

Mann-Whitney Test

Ranks

Stage		N	Mean Rank	Sum of Ranks
d-dimer	2	52	38.53	2003.50
	3	33	50.05	1651.50
	Total	85		

Test Statistics[a]

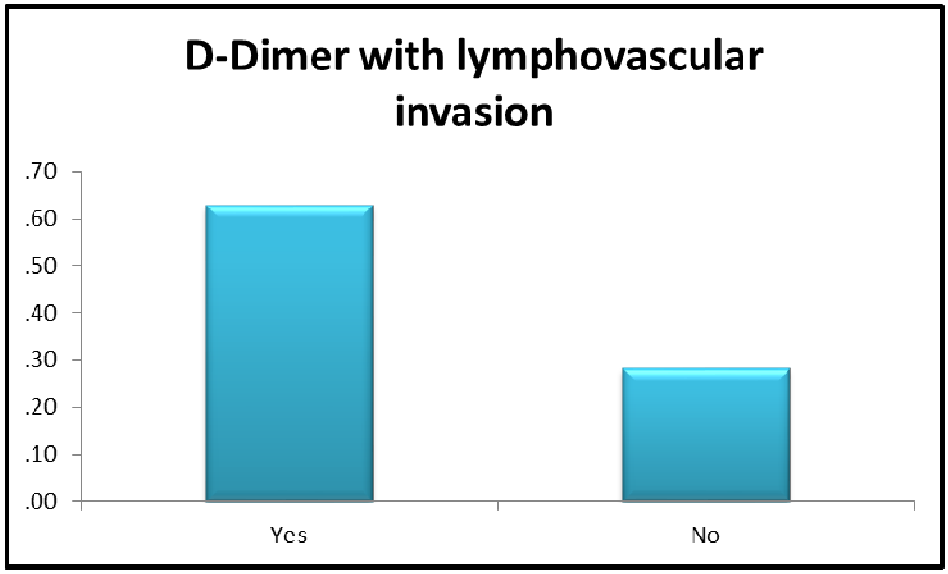
	d-dimer
Mann-Whitney U	625.500
Wilcoxon W	2003.500
Z	-2.100
Asymp. Sig. (2-tailed)	.036

a. Grouping Variable: Stage

T-Test

Group Statistics

lymphovascular invasion		N	Mean	Std. Deviation	Std. Error Mean
d-dimer	Yes	74	.63	.24	.03
	No	16	.28	.10	.02



Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% interval of the difference	
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
d-dimer	Equal variances assumed	11.540	.001	5.737	88	.000	.34696	.06048	.22677	.46715
	Equal variances not assumed			9.441	58.270	.0005	.34696	.03675	.27341	.42051

Crosstabs

Stage * lymphovascular invasion Crosstabulation

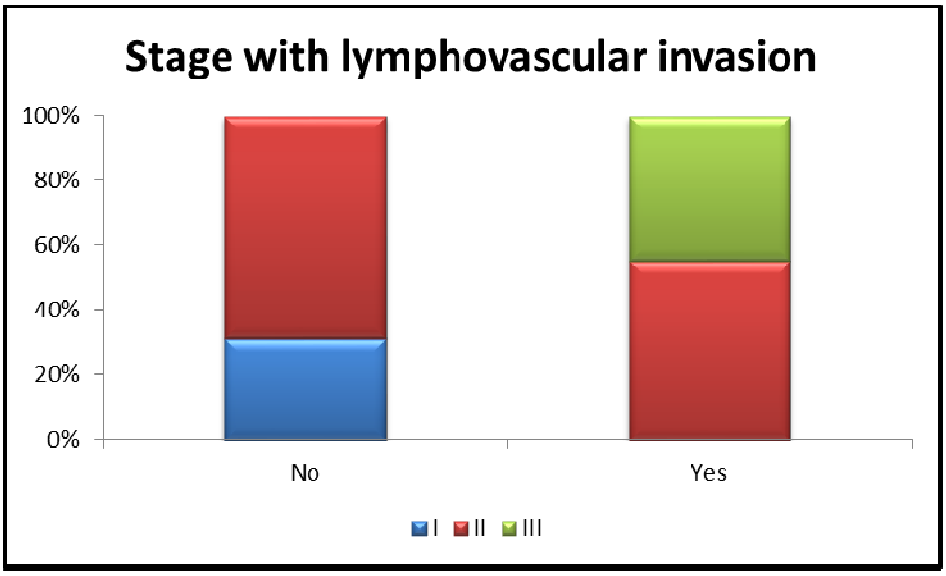
			lymphovascular invasion		
			No	Yes	Total
Stage	1	Count	5	0	5
		%	31.3%	0.0%	5.6%
	2	Count	11	41	52
		%	68.8%	55.4%	57.8%
	3	Count	0	33	33
		%	0.0%	44.6%	36.7%
Total		Count	16	74	90
		%	100.0%	100.0%	100.0%

	No	Yes
I	31.3%	
II	68.8%	55.4%
III		44.6%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	30.666[a]	2	.0005
Likelihood Ratio	30.579	2	.000
Linear-by-Linear Association	22.996	1	.000
N of Valid Cases	90		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is .89.



D-dimer being compared with stages of the Carcinoma breast using Krushal-Wallis test, results being No significance (p value >0.050) between d-dimer levels in stage I and stageII patients but highly significant (p value <0.01) between stage I and stage III and significant (0.01<p<0.050) between stage II and stage III.

By using t-test lymphovascular invasion present in 74 patients had mean d-dimer value and standard deviation being 0.63 and 0.24 respectively and with no lymphovascular invasion d-dimer value being 0.10, being statically significant (pvalue<0.0005)

7.DISCUSSION

Our study showed that maximum number operable carcinoma breast patients were stage II being 57.8%(52 out of 90 patients) and lowest being stage I 5.6%(5 out of 90 patients.

Lymphovascular invasion was found to be in 82.2%(74 out of 90 patients) and with no lymphovascular invasion in 17.8% (16 out of 90 patients).

In descriptive statistics, Minimum age of diagnosed carcinoma breast in our study was 35 years and maximum age being 75 years.

Minimum value of d-dimer was found to be 0.10ugFEU/ml and maximum valve being 1.24uFEU/ml with the mean value and standard deviation being 0.5678 and 0.25568 respectively

D-dimer being compared with stages of the Carcinoma breast using Krushal-Wallis test, results being No significance (p value >0.050) between d-dimer levels in stage I and stageII patients but highly significant (p value <0.01) between stage I and stage III and significant (0.01<p<0.050) between stage II and stage III.

In Blackwell et al study concluded a linear regression modeling showed relationship between the presence of lymphovascular invasion and elevated d-dimer levels[15].

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In hudhaifah shaker et al study, plasma d-dimer correlated with lmphovasuclar invasion and tumor size statistically significant but not significant with hormone receptor status[14].

8.CONCLUSION

Carcinoma breast requires prompt diagnosis and treatment to prevent cancer related deaths. Survival depends upon the stage of the disease at the time of diagnosis and lymph node status being an important prognostic factor[21].

Our study of D-Dimer with lymphovascular invasion in operable carcinoma breast clearly shows d-dimer levels increased in carcinoma breast patients especially with advancing stage of the tumor. Increased d-dimer can be considered as a potential biomarker for tumor size, lymph node involvement and lymphovascular invasion and early tumor metastasis in operable carcinoma breast[12].

Since d-dimer is a safe, easily available predictive and convenient marker it can be viewed as a potential prognostic marker for operable carcinoma breast.

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10.CLINICAL PERFORMA

•NAME:

•AGE:

•SEX:

•IP NO:

•DIAGNOSIS

-USG BREAST WITH AXILLA

-FNAC/CORENEEDLE BIOPSY

-USG ABDOMEN AND PELVIS/ XRAYS OF LONG BONES

-CECT CHEST/ CECT ABDOMEN AND PELVIS/ BONE SCAN

STAGE OF THE DIEASE:

• PRE-OPERATIVE D-DIMER LEVEL

•POST OPERATIVE HPE

-LYMPHOVASCULAR INVASION

11. MASTER CHART

s.no	name	age/f	ipno.	stage	d-dimer (ugm feu/ml)	lymphovascular invasion
1	vijaya	55	1843376	II	0.72	yes
2	parimala	38	1846918	II	0.22	no
3	saroja	62	1845719	III	0.8	yes
4	komala	60/f	1847534	II	0.6	yes
5	bhuvaneshwari	46	1847314	I	0.4	no
6	sugunya	54	1847685	III	0.9	yes
7	uma	43	1837157	III	0.66	yes
8	kanniyammal	58	1847283	III	0.8	yes
9	ayisha	37/f	1847283	II	0.3	no
10	malarvizhi	46	1857665	II	0.86	yes
11	lakshmi	65	1856038	III	0.74	yes
12	shanthi	49	1860412	III	0.66	yes
13	thulasi	63	1863108	II	0.38	yes
14	sundari	40	1864163	II	0.32	no
15	jaynathi	47	1844679	III	0.6	yes
16	kalaiselvi	57	1810041	II	0.2	yes
17	indumathi	45	1811488	III	0.56	yes
18	vijayalakshmi	43	1824061	II	0.48	yes
19	anjalai	39	1828646	II	0.22	no
20	banumathi	55	1829768	III	0.74	yes
21	vasantha	56	1822226	II	0.4	yes
22	revathy	40	1830553	II	0.2	no
23	rashitha	60	1836732	III	0.76	yes
24	mallika	50	1841404	II	0.8	yes
25	kannika	42	1841402	II	0.36	no
26	sumathi	35	1841393	III	0.82	yes
27	chinna ponnu	45	1839702	II	0.76	yes
28	kaveri	53	1843346	II	0.9	yes
29	pramila	42	1845011	II	0.66	yes
30	radha	55	1845055	III	1	yes
31	nivetha	40	1860112	II	0.8	yes
32	mohana	55	1800464	II	0.34	no
33	ponnuselvi	60	1801689	II	0.8	yes
34	chandra	38	1806322	II	0.56	yes
35	pradeepa	52	1812412	II	0.2	no
36	durga devi	49	1821934	III	0.74	yes
37	uma maheshwari	56	1825984	II	0.24	no
38	amirthavalli	40	1863676	II	0.8	yes
39	kavitha	43	1812421	III	0.3	yes
40	krishnaveni	60	1822999	II	0.36	no
41	velazhagi	45	1822944	II	0.34	yes
42	muthulakshmi	48	1823618	III	0.48	yes
43	soundarya	50	1828371	II	0.3	yes
44	lakshmi priya	40	1828367	III	0.38	yes
45	hemalatha	55	1829780	II	0.26	no

46	nagajothi	38	1829447	III	0.36	yes
47	navaj	40	1831528	II	0.2	yes
48	saraswathy	45	1831432	III	0.46	yes
49	kavya	58	1831931	II	0.2	yes
50	baby	41	1833149	III	0.24	yes
51	saranya	47	1832428	II	0.8	yes
52	janani	49	1884817	III	0.82	yes
53	nandhimi	40	1808029	II	0.74	yes
54	dhanasundari	65	1809232	II	0.76	yes
55	sathyavani	50	1853681	III	1.22	yes
56	gajalakshmi	57	1810534	II	0.84	yes
57	ganga	42	1820225	II	0.56	yes
58	rita	66	1824000	I	0.1	no
59	senthamari	54	1858331	III	1.24	yes
60	yamuna	59	1831536	II	0.84	yes
61	nagalakshmi	75	1841407	II	0.54	yes
62	neelavani	45	1828649	III	0.8	yes
63	malliga	60	1845980	II	0.56	yes
64	mala	55	1807964	I	0.3	no
65	rajeshwari	39	1810753	III	0.4	yes
66	vijaya	35	1835405	II	0.38	yes
67	rajalakshmi	54	1810724	II	0.48	yes
68	ponni	46	1812197	III	0.36	yes
69	angammal	50	1819207	II	0.2	yes
70	pachaimaal	55	1819195	III	0.22	yes
71	muthurani	48	1819356	II	0.34	yes
72	tamilselvi	55	1820236	II	0.2	yes
73	mukkammal	45	180083	II	0.7	yes
74	mumtaz begum	45	1845694	III	0.66	yes
75	sowkath	46	1800753	II	0.64	yes
76	devaki	38	1809788	III	0.9	yes
77	ethiyammal	38	1819986	I	0.2	no
78	kalyani	50	1819488	II	0.6	yes
79	adhilakshmi	53	1812236	III	0.72	yes
80	radhika	47	1800541	II	0.9	yes
81	rani	47	1821231	II	0.86	yes
82	nadhiya	62	1822203	II	0.6	yes
83	maheshwari	42	1832042	III	0.52	yes
84	shantha	45	1825007	II	0.76	yes
85	jayantha	59	1824960	III	0.66	yes
86	rose	57	1825452	II	0.74	yes
87	kala	40	1826165	I	0.5	no
88	marilakshmi	54	1829469	III	0.6	yes
89	sangeetha	45	1835026	II	0.86	yes
90	manonmani	55	1877810	III	0.8	yes